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THE BRITISH JOURNAL OF DISEASES OF THE CHEST
Published in Association with the British Thoracic Association

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Hypothesis

THE NATURAL HISTORY OF LUNG CANCER: A REVIEW BASED ON RATES OF TUMOUR GROWTH

D. M. Geddes

Brompton Hospital, London

Out of 100 patients with lung cancer discovered, fewer than 10 will live five years. Eighty will have inoperable disease at the time of diagnosis and most of these will die within three years; only one or two will be alive after five years. The 20 patients with localized disease will have an operation and about six of them will be alive after five years. These statistics have not changed over the past 30 years and this is in spite of many attempts at earlier diagnosis as well as a considerable improvement in operative mortality.

In the face of these gloomy statistics there is a surprising lack of information about the natural history of the disease. There are no proper controlled studies of unselected patients in the literature. The few studies which have included an untreated control group have always been done on 'inoperable' patients, i.e. those with the most advanced disease. Trials of radiotherapy and chemotherapy show very little, if any, benefit in terms of survival and untreated control patients sometimes do better than those who are treated (Laing et al. 1975).

The role of surgery appears at first sight to be better defined. Surgery is better than radiotherapy for squamous but not for oat-cell carcinomas (Morrison et al. 1963; Miller et al. 1969). However, since patients with early localized disease are considered to be curable, treatment cannot be withheld in the interests of a controlled trial. The result is that the natural history of limited operable disease is unknown. Radiotherapists and chemotherapists can justifiably complain that their treatment is never given to the patients with the best prospects of cure.

Against this background of doubt about the best form of treatment, and certainty that most treatment is ineffective, is the obvious need for a better understanding of the natural history of the disease. Such understanding should help in three ways. First in assessing the true value of existing treatments. Second in judging an individual patient's prognosis and so in choosing the most appropriate treatment. Third, and most important, in planning a rational search for new and more effective forms of treatment.

We have used the considerable literature on tumour growth rates in lung cancer in an attempt to calculate the natural history of the disease.

EXPONENTIAL MODEL OF TUMOUR GROWTH

This hypothesis was first suggested by Collins et al. in 1956. The hypothesis assumes a tumour to start from a single cell. This cell then divides to become two cells, each of which divide to become four, eight, sixteen and so on. If this process goes on at a constant rate, then the tumour growth will be exponential and its volume at any time can be easily calculated. The simplest way to describe the growth rate is the volume doubling

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time—the time taken for the tumour volume to double. Exponential tumour growth is analagous to the exponential decay of a radioactive isotope. Growth is described by doubling time where decay is described by half-life.

At its simplest, this model predicts that a single cell of 10 μm will become a tumour of 1 mm in diameter after its volume had doubled 20 times. A further ten doublings will produce a tumour of about 1 cm in diameter and after ten more doublings, the tumour will have a diameter of 10 cm with a total mass of 1 kg. This is shown in Fig. 1. This figure shows how a tumour appears to be small and slow-growing for the majority of its life until it reaches a diagnosable size when it appears to grow very rapidly. In fact, the rate of tumour growth is relatively constant throughout its life and compared with other tissues is rather slow. (The vast majority of cancers grow very much more slowly than a human thumb-nail (Spratt & Spratt 1976).) Tumour growth is like the reward demanded in the Arabian legend: one grain of corn for the first square on the chess board, two for the next, four for the next, etc. The amount of grain on the sixty-fourth square exceeds the total world production of corn since the beginning of mankind.

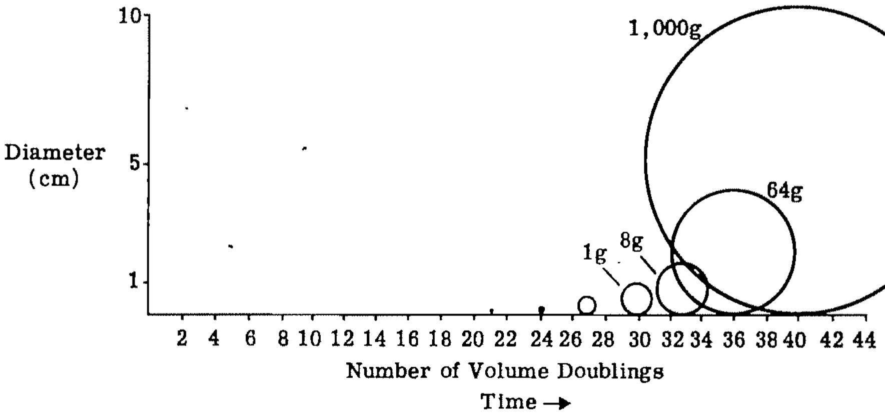


Fig. 1. The life of a solid tumour. Time is expressed as volume doublings. A tumour with a doubling time of 1 month takes 40 months to reach 10 cm diameter, while another with a doubling time of 1 year takes 40 years

Tumour doubling time (T_2) for the model may be calculated from two diameter measurements separated by a known time or more simply may be derived from Fig. 2. The mathematics of the model are discussed in the appendix.

Validation of the model

This model of tumour growth can be validated in the following ways:

Measurement of doubling times. If a tumour grows at a constant exponential rate, then its doubling time will be constant. Doubling times have been calculated for many lung tumours, both primary and secondary, from serial chest radiographs. The vast majority of observations show the doubling times of individual tumours to be constant. Whenever doubling times have been shown to change, they tend to become longer towards the end of the tumour's life. In other words, the tumour growth rate slows as the tumour gets larger. A review of published series shows that 80–90% of tumours grow exponentially.

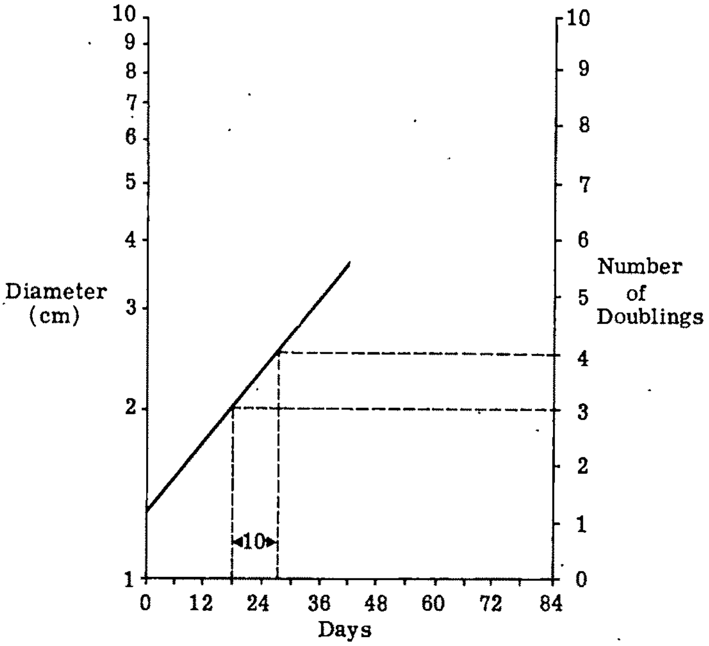


Fig. 2. Chart for measuring tumour doubling time. Tumour diameter is plotted on a logarithmic scale against time. Using the right-hand scale one volume doubling can be marked on the growth curve and the doubling time read from the time scale

Observations on Wilm's tumour. This elegant study by Collins et al. (1956) formed one of the corner-stones of their hypothesis of exponential growth. An embryonic tumour must have begun at or after the time of conception of the child. The tumour then took a known length of time to manifest itself clinically. The maximum time from one cell to diagnosis is therefore the age of the child at diagnosis plus nine months. If the tumour is then removed surgically and one cell is left behind, this cell continues to grow at the same, rate as the original tumour. After the same time interval, i.e. age at diagnosis plus nine months, any recurrence will be the same size as the original tumour and should be clinically obvious. If the child is well at this time then he is cured. 206 case histories of children with surgically treated Wilm's tumour were reviewed. The tumour had recurred in 137 children and in every case this was within their theoretical period of risk. Forty-nine patients had been free of disease for longer than the risk period and none of these suffered a recurrence subsequently.

Animal studies. Tumour growth rates have been plotted in animals and show exponential growth with a tendency for slowing of growth as the tumour gets large (Dethlefsen et al. 1968). Acceleration of growth is not seen. Some of the tumours studied are very different from naturally occurring disease in man and so these studies have to be interpreted with caution. Nevertheless, the broad principles of exponential growth are confirmed.

Objections to the model

There are some objections to the exponential model:

Doubling times may not be constant during the microscopic period of tumour growth. Some tumours have doubling times which are so long that back extrapolation provides the absurd conclusion that the tumour began many years before the individual was conceived. This is probably a reflection of the slowing of tumour growth with size referred to above. This applies to only a few tumours but nonetheless estimates of starting time of a tumour by back extrapolation must be seen as only approximate. This objection is less important for extrapolation forward over a few tumour doublings.

Metastases. Can observations on the primary tumours be applied to its metastases? Metastases seem, in general, to grow faster than their primary. The evidence for this is limited and information for primary lung tumours very scanty indeed (Brenner et al. 1967). Nevertheless, variation in growth rates between the primary and metastatic tumour will introduce inaccuracy into any calculations based on the growth of the primary alone. This inaccuracy will be greater for oat-cell tumours, which metastasize widely early, than for squamous and adenocarcinomas.

The exponential model then fits the observed facts reasonably well. Exceptions will occur when the centre of a tumour breaks down, when tumours are under hormonal control, as a result of treatment and, rarely, when spontaneous regression occurs. From this model the natural history of a tumour can be calculated by extrapolation. Extrapolating back in time gives an approximate date for malignant change (when the first malignant cell arose); while extrapolation forward to a total of 40 doublings, when there will be about 1 kg of tumour, gives an approximate date of death. This is summarized in Table I.

Table I. The natural history of a solid tumour which grows exponentially

Doublings	*Cells*	*Diameter*	
0	1	10 μm	Microscopic
20	10^6	1 mm	Microscopic
30	10^9	1 cm	Detectable on chest radiograph
35	$10^{10.5}$	3 cm	Average diagnosis
40	10^{12}	10 cm	Death

Calculating the natural history

To do these calculations, three properties of tumour need to be known: doubling time, size and total tumour mass at death.

Doubling time. Reports of doubling times of 228 primary lung cancers in the literature are listed by cell type in Table II. Doubling times show a log-normal distribution and so the geometric mean and standard deviation have been calculated. The distribution of histological types among these 228 reported tumours shows 48% squamous, 26% adeno-, 19% undifferentiated carcinoma and 7% miscellaneous. This distribution is relatively close to the overall incidence of different cell types in lung cancer.

Size. Fig. 3 shows the distribution of sizes of peripheral tumours at diagnosis taken from four published series. This distribution is log-normal and the mean diameter

Table II. Reports of doubling times for primary lung cancer*

	Squamous	*Adeno*	*Undifferentiated*	*Oat*	*Other*	*Total*
Brenner et al. 1967	3		1			4
Breur 1966	2					2
Chahinian 1972	21	3		3		27
Garland et al. 1963 and Garland 1966	36	12	9		3	60
Meyer 1973	11	7	1	2	1	22
Schwartz 1961	10	2				12
Steele and Buell 1973	16	24	23		4	67
Weiss et al. 1966 and Weiss 1974	12	12	8		2	34
Total	111	60	42	5	10	228
Log mean T_2	4.476 ±0.725	5.084 ±0.815	4.456 ±0.596	3.362 ±0.540	—	4.621 ±0.791
Mean T_2 (days)	88	161	86	29		102

* Figures represent the number of tumours measured

(geometric) is 3.1 cm. The larger series of Steele and Buell (1973) has not been included because they selected tumours under 6.0 cm in diameter. However, the mean size of the 303 peripheral tumours is 3.0 cm, which agrees well with the other series. Two large surgical series (Slack et al. 1972; Soorae & Abbey-Smith 1977) have reported tumour size and this is given as greatest diameter. These show a mean greatest diameter of 4.0 cm from a total of 1282 cases. Most tumours are not spherical, but wedge-shaped or

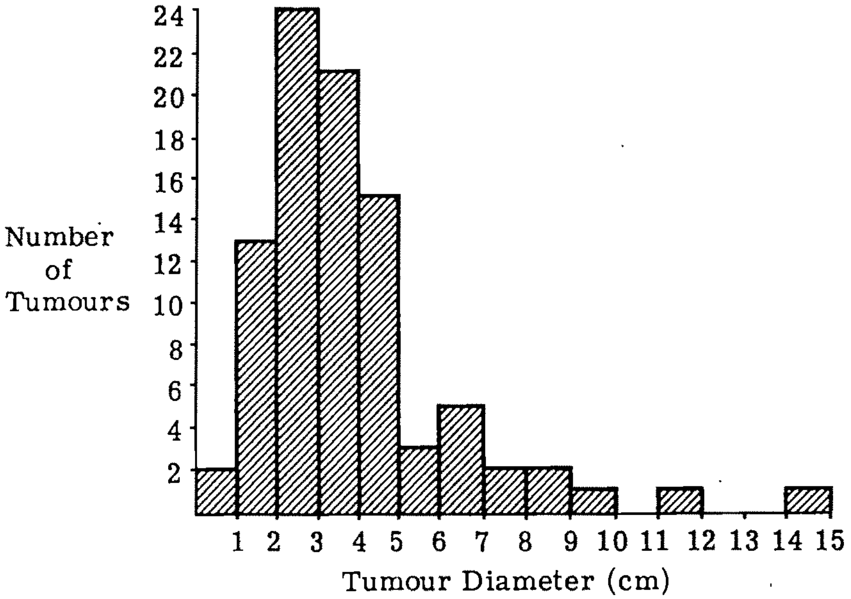


Fig. 3. Distribution of sizes of 90 primary lung tumours at diagnosis. Data from Chahinian (1972), Meyer (1973), Schwartz (1961) and Weiss (1971)

cylindrical, and a cylinder 4 cm by 2 cm has the same volume as a 3 cm sphere. The mean diameter of 3.1 cm from Fig. 3 therefore agrees well with the surgical series. We have taken this distribution of sizes to be reasonably representative of tumours at diagnosis.

Tumour mass at death. Direct measurements of total tumour mass are impossible because the total mass of microscopic metastases is unknown. However, from the tumour growth diagram in Fig. 1 it can be deduced that death will occur within a relatively narrow range of doubling times. After 35 doublings, a 4 cm diameter tumour with a total mass of about 30 g is most unlikely to cause death unless it is in some critical site. At the other end of the scale, after 45 doublings, a tumour will have a total mass of 32 kg at which time survival is inconceivable. Death will therefore occur sometime between these two extremes. A total tumour mass of 1 kg has generally been taken to cause death and this is equivalent to 40 tumour doublings. The three series reported which allow the calculation to be made all show the mean time of death to occur very close to 40 doublings (Table III). Obviously, there will be some variation about this mean figure with some patients dying with small critically placed metastases, while others survive with massive intrathoracic tumours. However, the variation in terms of doublings will be small.

Table III. Number of volume doublings at death

		n	*Mean doublings to death*
Breur 1966	Lung metastases	79	39.5
Schwartz 1961	Lung primary	13	41
Spratt and Spratt 1964	Lung metastases	118	39

Calculation. N_d = number of volume doublings to reach a tumour diameter $d_{om} = 10 \log_{10}{}^{d} + 30$.
Volume doublings at death = N_d + survival from d_{om}/T_2.

We have used these data on doubling times, tumour size and tumour mass at death to calculate the natural history of lung cancer. This is summarized in Table IV. If all the doubling times of lung cancer in the literature are pooled, then the time from malignant change to diagnosis is about 10 years, and following diagnosis, the average time to death is about 18 months.

PREDICTED SURVIVAL

The simplest situation is to consider a single tumour with a known doubling time and size. Predicted survival can be calculated from Fig. 4. This shows that both size and doubling time have a profound influence on survival. For example, a tumour with the average doubling time of 100 days will cause death within four months if it is diagnosed when its diameter has reached 8 cm, but the same tumour diagnosed as a 1 cm nodule would not be expected to cause death for nearly three years. Similarly, a 2 cm cancer will cause death in seven months when it has a doubling time of 30 days (e.g. an oat-cell carcinoma) while a patient with the same sized tumour with a doubling time of 300 days (e.g. a slow-growing adenocarcinoma) will survive for over five years without treatment.

Table IV. Natural history of untreated lung cancer

Histology	*n*	*Mean* T_2 (days)	*Years from malignant change to* Earliest Diagnosis (1 cm)	Usual Diagnosis (3 cm)	Death (10 cm)
Squamous	111	88	7.2	8.4	9.6
Adenocarcinoma	60	161	13.2	15.4	17.6
Undifferentiated	44	86	7.1	8.2	9.4
Miscellaneous	8	—	—	—	—
All	228	102	8.4	9.8	11.2
Oat cell	5	29	2.4	2.8	3.2

Any group of tumours will have a range of sizes and doubling times. Predicted survival curves from time of diagnosis for different sized tumours based on the distribution of doubling times in Table II are shown in Fig. 5. By combining these curves according to the distribution of tumour sizes at diagnosis from Fig. 3 predicted survival curves from diagnosis can be calculated. These are shown in Fig. 6. This represents the survival of an overall group of patients with lung cancer. The curves for different histological

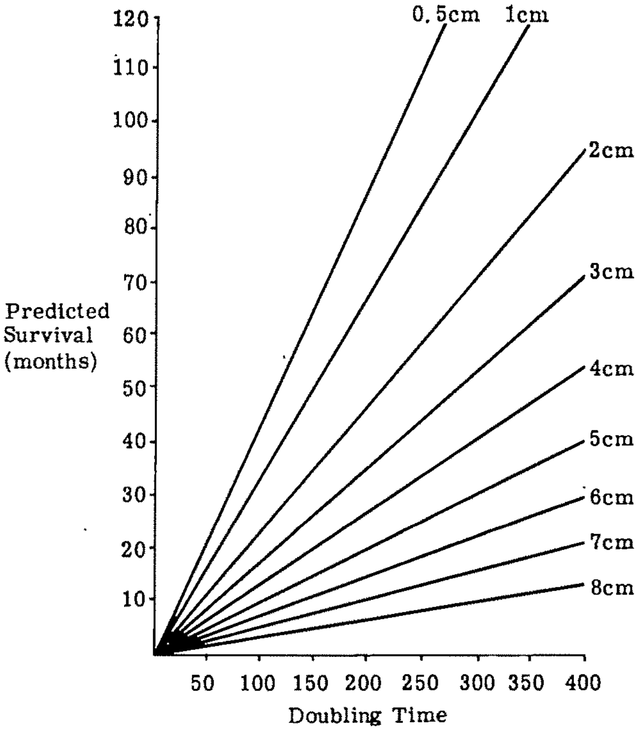


Fig. 4. Predicted survival for tumours according to size and doubling time. *Calculation*: The predicted survival to 40 volume doublings is $(40-N_d)T_2$, i.e., $10T_2\ (1-\log_{10}d)$

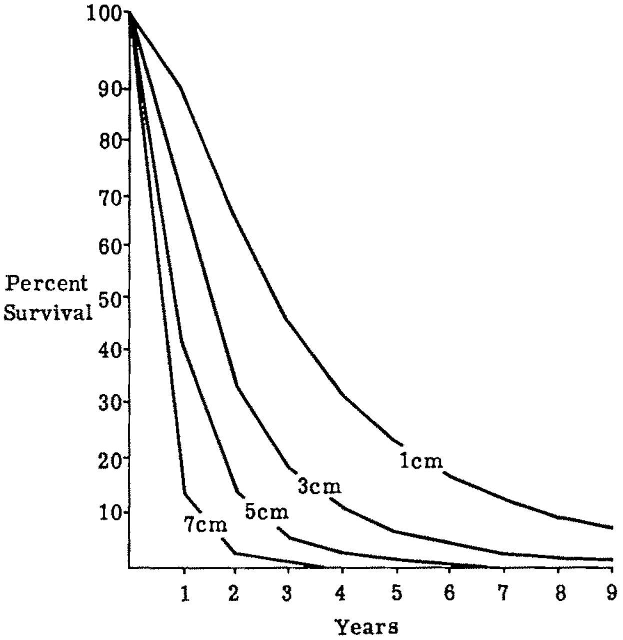


Fig. 5. Predicted survival curves from time of diagnosis for different tumour sizes. *Calculation:* To survive to time *t*,

$$T_2 \geqslant \frac{t}{10(1-\log_{10}d)}$$

From the distribution of doubling times in Table II, the percentage with equal or longer T_2 is calculated for each value of *t*

types of tumour show marked differences with adenocarcinomas surviving longer than squamous tumours. Oat-cell carcinomas have been included, but because of the paucity of data, the curve is at best approximate.

CLINICAL CORRELATIONS

Long latent period

This is at first sight surprising but helps to explain some of the puzzling features of the disease.

Date of the first abnormal chest radiograph. Direct evidence comes from the study of Rigler et al. (1953) who questioned the relatives and doctors of 264 patients with lung cancer in order to find out how many had had previous chest radiographs. Fifty such patients were identified and the old films were then reviewed. Radiographic abnormalities which long preceded diagnosis were found in most cases. One patient lived nine years from the first radiographic change to operation and another had a peripheral carcinoma visible on radiography more than four years before his first symptom. In the 13 patients with operable disease, the first radiographic abnormality preceded surgery by an average of three years.

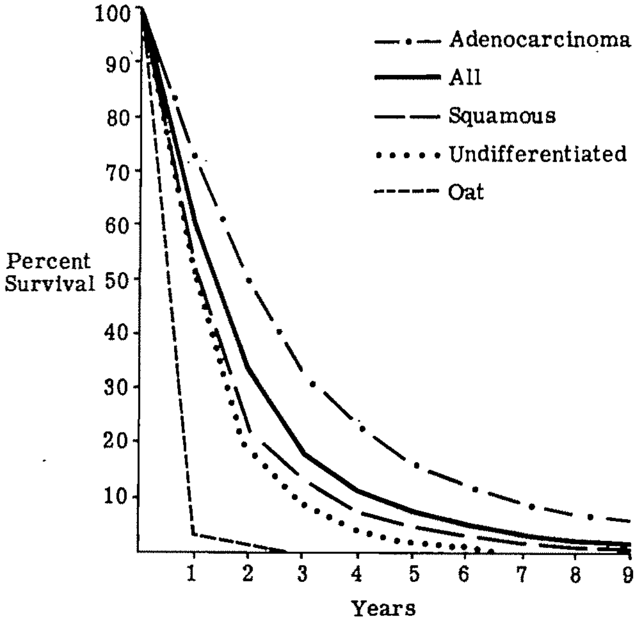


Fig. 6. Predicted survival curves from time of diagnosis according to histology. *Calculation*: The survival curves in Fig. 5 were combined according to the distribution of sizes in Fig. 3

Age at onset. Table IV suggests that lung cancer is diagnosed on average about 10 years after malignant change has occurred. Since the peak incidence of the disease is at the age of 60, malignant change must occur around the age of 50. Since a smoker usually starts in his teens, he smokes for about 30 years without developing the disease. The long delay between application of the carcinogen and malignant change is puzzling. It suggests that prolonged stimulation is necessary to produce malignancy or that there is some efficient anti-tumour defence system which becomes less effective with age. Increasing inefficiency of immunosurveillance might be responsible. In practice, it means that a young smoker who gives up the habit after 10 years of smoking should have only a very slight risk of developing lung cancer. It is therefore interesting that Doll and Peto (1976) showed no increased risk of the disease in doctors who stopped smoking before the age of 30.

Age and aggressiveness of cancer. If two men both develop malignant change at the age of 40 years, and doubling time of one tumour is 30 days and of the other 300 days, then the fast-growing tumour will present after about three years, while the slow-growing tumour will present after 30 years. So one man will have an aggressive cancer at the age of 43 years, while the other will have relatively benign disease at the age of 70 years. This accords well with clinical experience of lung cancer. Steele and Buell (1973) showed that lung cancer in young patients had shorter doubling times.

Recurrent cancer after surgery. Usually a patient is considered cured if he is free of disease five years after his operation. However, reports of long follow-up after surgery are littered with 'second', and 'third' and even 'fourth' primaries (Shields & Robinette 1973; Abbey-Smith et al. 1976). Two observations suggest that many second primaries are recurrences. First, the incidence of second 'primaries' seems to fall off with time, so that after 10 years, they are almost unknown. This 10 years is the time needed for a single malignant cell left at operation to grow to a diagnosable tumour. Secondly, the later the 'second primary' develops, the more benign it appears to be. This is to be expected if the 'second primary' is a recurrence: the reason it presents late is precisely because it grows slowly.

Table V. Lung cancer deaths after stopping smoking

Years after stopping smoking	*Deaths in ex-smokers divided by No. expected in non-smokers*	
	Observed*	Predicted
0	15.8	—
<5	16.0	15
5–9	5.9	11
10–14	5.3	6
≥15	2.0	2

* Doll and Peto (1976).

Calculation. For 100 deaths occurring at year 0 the number of tumours beginning in each preceding year were calculated from the distribution of doubling times (time to death $= 40 \times T_2$). For each year after stopping smoking the contribution of the preceding year to total deaths was deleted. Total deaths expected in each year were then compared with those in year 0 and the 16:1 risk reduced accordingly. For this calculation adenocarcinomas were excluded since they are not associated with smoking.

Stopping smoking. After stopping smoking, the risk of lung cancer remains high for some time and is still nearly twice that of life-time non-smokers after 15 years (Doll & Peto 1976). Table V shows the increased risk of lung cancer for ex-smokers according to the number of years they have stopped smoking and this is very similar to the increased risk as calculated from doubling times. If malignant change stops as soon as smoking stops, more than 10 years are then needed before all tumours which have just begun are large enough to cause death.

Survival curves

Fig. 6 shows survival curves for all tumours and for each cell type. These curves give an indication of the survival which might be expected in an untreated group of patients with lung cancer. Detailed comparison between these curves and actual survival curves is probably not justified but they illustrate a number of important points.

Correlation of survival with cell type. Oat-cell carcinomas have the shortest prognosis while adenocarcinomas have the longest. Squamous cell and undifferentiated carcinomas, other than oat-cell, occupy a middle position. This agrees well with the observations of Hyde et al. (1973) on the natural course of inoperable cancer in 7500 patients.

Comparison with observed survival figures. Five-year survival in lung cancer varies from 5 to 9%. This prognosis is similar to that predicted from growth rates. There are two main differences: the predicted survival figures show less early mortality and then after five years the actual survival figures are better. These differences are partly technical, since the distribution of sizes used is likely to be biased towards small tumours and this will reduce early mortality. Also, the time of death is taken as exactly 40 doubling times when in reality this will be distributed between 35 and 45 doubling times. The effect of its variation around 40 will be to increase early and reduce late mortality. After allowing for these technical inaccuracies, the better 5–10-year survival figures obtained in practice may represent the effect of treatment. Such an effect is, however, obviously very small. Slowing of tumour growth is another explanation.

The effect of staging. Staging selects tumours into groups on the basis of size and spread and is likely to select for doubling time as well. Small slow growing tumours will show good survival figures on the basis of natural history alone and these good figures may be falsely attributed to treatment. This is discussed in more detail in the next section. The important conclusion is that survival figures from staged disease must be interpreted with caution.

Treatment

Radiotherapy and chemotherapy. Trials with untreated controls have been done for radiotherapy and chemotherapy. This is obviously the best method of assessing any therapy and so predicted survival based on growth rates has little extra to offer. Indeed since these trials show that treatment may actually be harmful (Laing et al. 1975) it is difficult to understand why an untreated control group is not considered obligatory. In the absence of controls, growth rates may have some value. Chahinian and Israel (1969) pointed out that a drug may be effective without necessarily making a tumour disappear. The drug may slow the growth rate and so prolong survival. They therefore suggested the concepts of survival gain and volume gain as mathematical tools to evaluate treatments. In summary, this involves calculating the survival of the patient on treatment over and above that predicted from the growth curve of his tumour. This might help investigators to recognize a potentially valuable drug.

The theoretical implication of this model of tumour growth is that a treatment killing 99% of all cancer cells in the body will succeed only in reducing 10^{12} tumour cells to 10^{10}. This is equivalent to about seven volume doublings. An oat-cell tumour with a doubling time of 20 days will therefore have been set back a mere 4–5 months. A 90% cell kill is equivalent to about three doubling times and so the benefit may be almost unnoticeable.

Surgery. There are no trials with an untreated control group, but there are a few reports of 'operable' patients who have not had surgery. Smart (1966) showed a 22% five-year survival in such patients treated with radiotherapy which suggests that there may be little difference between the two managements. The obvious untreated 'control' patients are those who are considered operable but who refuse or are unfit for operation.

Surprisingly, there is very little information on such patients in the literature. Boucot et al. (1967) reported 12 such patients from the Philadelphia pulmonary neoplasm research project with a median survival of 19 months, median survival in 23 patients with curative resections was little better at 22 months. Weiss and Boucot (1977) reported 48 patients with lung cancer originating as round tumours, again from the Philadelphia project. After excluding postoperative deaths, there was no difference in terms of survival between resected and unresected cases. Three of the four patients living longer than five years were in the unoperated group. Both these studies can be criticized, the first because of a high operative mortality, the second because of lack of histology in some patients. However, they raise serious doubts about the role of surgery.

Selection of patients for surgery. Surgical patients are inevitably highly selected. Limited disease will select for small tumour mass and so the tumour will be further back on its growth curve. Lack of local invasion or distant metastases are likely to select slow-growing tumours both because fast growers metastasize sooner and also because any metastases will be clinically obvious sooner if they grow fast. The delay between first symptom and surgery will allow fast-growing tumours to invade and become 'inoperable' while slower-growing tumours will have changed little. Finally, the general condition of the patient will be a reflection of the doubling time of the tumour. Patients who are symptom-free are likely to have tumours with long doubling times (Chahinian 1972).

The effect of selecting for slow-growing tumours will be to improve survival figures. This is shown in Fig. 7. Here we have arbitrarily taken the longest 25% of the doubling times in the literature and calculated a survival curve based on tumour growth. By

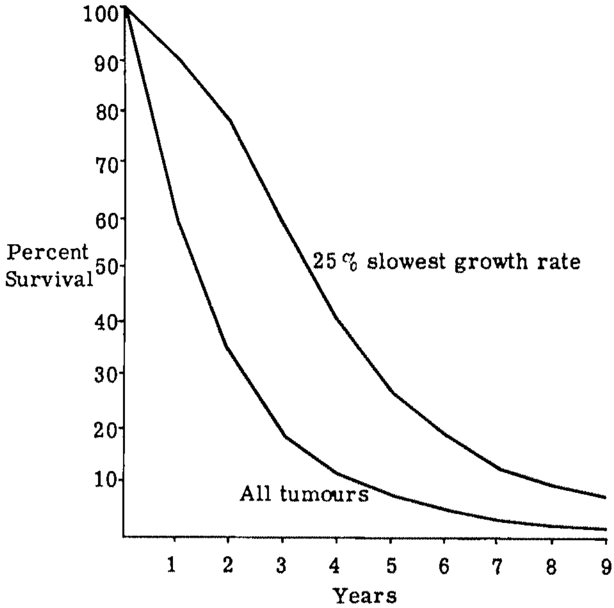
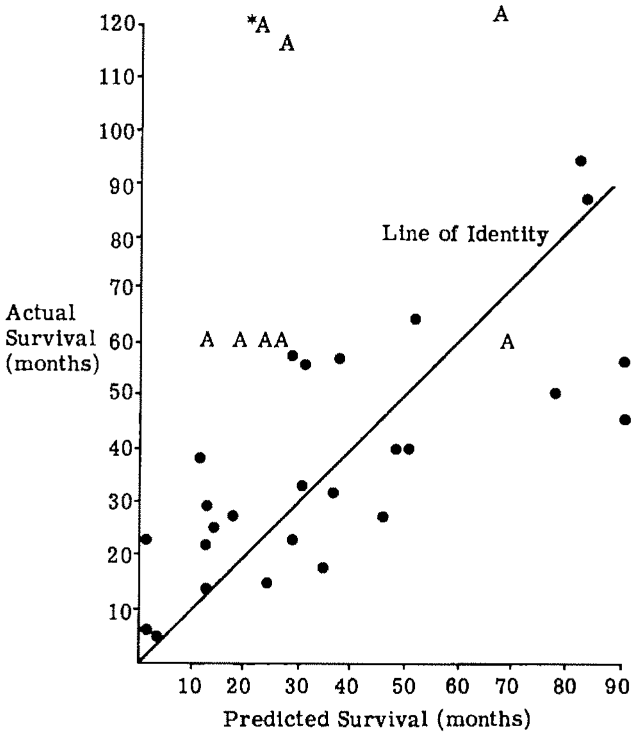


Fig. 7. Predicted survival curves for all tumours and for the 25% with longest doubling times selecting patients in this way, 28% five-year survival and 4% ten-year survival can be achieved.

Comparison of predicted with actual survival after surgery. The best way to estimate the true effect of surgery is to compare predicted with actual survival in patients in whom tumour size and doubling time have been recorded before operation. Weiss et al. (1966) have reported 18 such patients from the Philadelphia project and Meyer (1973) reported a further 17. The predicted survival of these patients has been taken from Fig. 4 and is compared with their actual survival in Fig. 8. This graph shows that patients dying from recurrent tumour survive only as long as their tumour growth predicts.* In other words surgery, in spite of removing the obvious tumour mass, has not prolonged survival significantly. If only a few cells were left behind at the operation site, then a long latent



*Died of Myocardial Infarct, tumour free
A = Alive

Fig. 8. Survival following resection of lung cancer. Predicted and actual figures compared

period would be expected before the recurrent tumour was clinically apparent. Late recurrence with improved survival would then be expected. The fact that there is no improvement in survival suggests that a mass of tumour similar to that removed has been left behind. All these operations were 'curative', i.e. as far as the surgeon could tell the tumour had been removed completely. The tumour mass left behind must therefore be in the form of distant metastases. It is difficult to avoid the conclusion that in 27 of these 35 patients with small peripheral tumours, distant metastases were present at the time of operation.

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* The correlation between predicted (x) and actual (y) survival by least squares regression is $y=16+0.6x$ ($r=0.76$, $P<0.001$). The slope is significantly different from 1. Patients dying soon after operation survive a little longer than predicted while those dying more than 40 months after operation tend to die earlier than predicted. This may represent early benefit from removal of tumour mass which is later reversed by the tendency of metastases to grow faster than the primary. However, these few observations do not allow any definite conclusions.

Eight patients were still alive at the time of the reports. Seven of these are in the top left-hand quarter of the graph, well separated from the patients who died. These represent surgical cures. It is possible that one cell left behind at operation will still lead to a recurrence and death up to 40 doubling times later and a patient cannot be confidently pronounced cured until this time has passed. Of the eight patients alive, only one has lived this long.

This analysis is based upon an exponential model of tumour growth. If any primary lung cancers deviate from exponential growth and grow more slowly as they get older, their natural history will be prolonged and they may not cause death for many years, if at all. Such tumours will tend to be operable and so will contribute to surgical survival figures. It is chastening to realize that if only 5% of all tumours were to behave in this way, the majority of five-year survivors could be expected on tumour natural history alone.

CONCLUSIONS

About seven-eighths of a tumour's life will have passed when it is diagnosed. The vast majority, and perhaps all tumours, will be disseminated at this time. It is therefore not surprising that treatment is so unsuccessful and in particular that local treatment has so little to offer. How then can the dismal picture of lung cancer be improved?

Earlier diagnosis

Attempts at population screening by chest radiography to detect cases early have proved both costly and ineffective. Many have largely been abandoned. The best that could be expected from such programmes is to diagnose the tumour a few doubling times earlier. Cancer which has been present some 7–10 years before diagnosis is hardly likely to be affected by bringing that date forward a few months. Some much more sensitive technique would be needed to detect a clump of malignant cells 1 mm in diameter. It is clearly unrealistic to expect this sensitivity from chest radiographs or scans. A more optimistic approach is to identify a circulating specific tumour marker, biochemical or immunological. This might allow much earlier diagnosis, but the problems of establishing the relevance of such a marker in an apparently healthy patient are formidable: once established, it is difficult to see what one would do next.

Treatment

Systemic treatment is needed to treat disseminated disease. When effective drugs or immunotherapy are discovered, it will be logical to use them as early as possible when the tumour mass is smallest. The role of surgery may then need to be redefined as another effective means of reducing tumour mass rather than as curative treatment in its own right. Joseph et al. (1971) have reported excellent controlled studies of resection of pulmonary metastases from a range of primary tumours. They showed that resection prolonged survival and this was especially striking for tumours with the longest doubling times. Surgery in some of these patients may be reducing tumour mass so much that the patients' own immunological defences are capable of controlling the remaining disease. In primary lung cancer the place of surgery as an adjunct to effective systemic therapy must remain uncertain until such therapy is discovered.

Prevention

Lung cancer is a preventable disease. At present it is virtually untreatable and in view of its natural history may remain so. It is, then, easy to see where the bulk of any research effort should be aimed. How can people be persuaded not to start smoking? Once started, how can they be helped to stop? Are there any innocuous alternatives? Is there an identifiable genetic group predisposed to lung cancer? Is there any form of immunotherapy which would prevent the development of the disease rather than treat it when it is too late?

Control of the present lung cancer epidemic lies in the answers to these questions.

APPENDIX: THE MATHEMATICS OF TUMOUR GROWTH

Exponential model

The volume, V, of a sphere diameter, d, is:

$$V=\frac{\pi}{6}d^3 \qquad (1)$$

Where a tumour grows from V_0 to V_t in time t, the volume at time t can be calculated using the exponential coefficient, b:

$$V_t=V_0\ e^{bt} \qquad (2)$$

By expressing the volume in terms of diameter (equation 1), equation 2 becomes:

$$\frac{\pi}{6}d^3{}_t=\frac{\pi}{6}d^3{}_0\ e^{bt}$$

which is:

$$d_t=d_0\ e^{\frac{bt}{3}}$$

solving for b:

$$b=\frac{3\log d_t}{t\log d_0}=\frac{3}{t}\log\left(d_t/d_0\right) \qquad (3)$$

Tumour doubling time (T_2) is the time for the tumour volume to double, i.e.:

$$V_t=2V_0$$

$$\therefore\ 2V_0=V_0\ e^{bT_2}$$

solving for T_2

$$\log 2 = bT_2$$

$$T_2 = \frac{\log 2}{b}$$

substituting for b (equation 3):

$$T_2 = \frac{t \log 2}{3 \log d_t/d_0}$$

Thus, T_2 can be calculated from two diameter measurements, d_0 and d_t, separated by interval t.

Other models

As a result of studies with animal tumours, it is evident that the Gompertzian function

$$V = V_0 \exp\left[\frac{A}{a}(1 - e^{-at})\right]$$

describes tumour growth better (Laird 1964) (a = deceleration parameter; A = growth parameter). This expression is essentially exponential growth with a tendency to decelerate with time. Tumour growth slows as the tumour enlarges.

Another approach is the relationship $dM/dt = kM^b$ where M is the tumour mass and b the exponent. When $b = 1$, this represents exponential growth and $b = 0$ is linear growth. From a study of many hundreds of mouse mammary tumours, Dethlefsen et al. (1968) found a value of $b = 0.72$ to describe tumour growth best. There are insufficient data to establish whether these more complicated equations describe tumour growth in man. Certainly an exponential model may oversimplify tumour growth, but for the purposes of this review, the simple relationship is preferred. All the more complicated expressions show a slowing of tumour growth with time. This will tend to prolong predicted survival.

ACKNOWLEDGEMENTS

I am particularly grateful to David Brown who performed all the calculations, as well as giving invaluable and intelligible mathematical and statistical advice. I am also greatly indebted to Dr L. D. Hill, Dr S. Spiro and Dr Gordon Steele for detailed and constructive criticism of the manuscript, and to Heather Rolls for the speed and accuracy of her typing.

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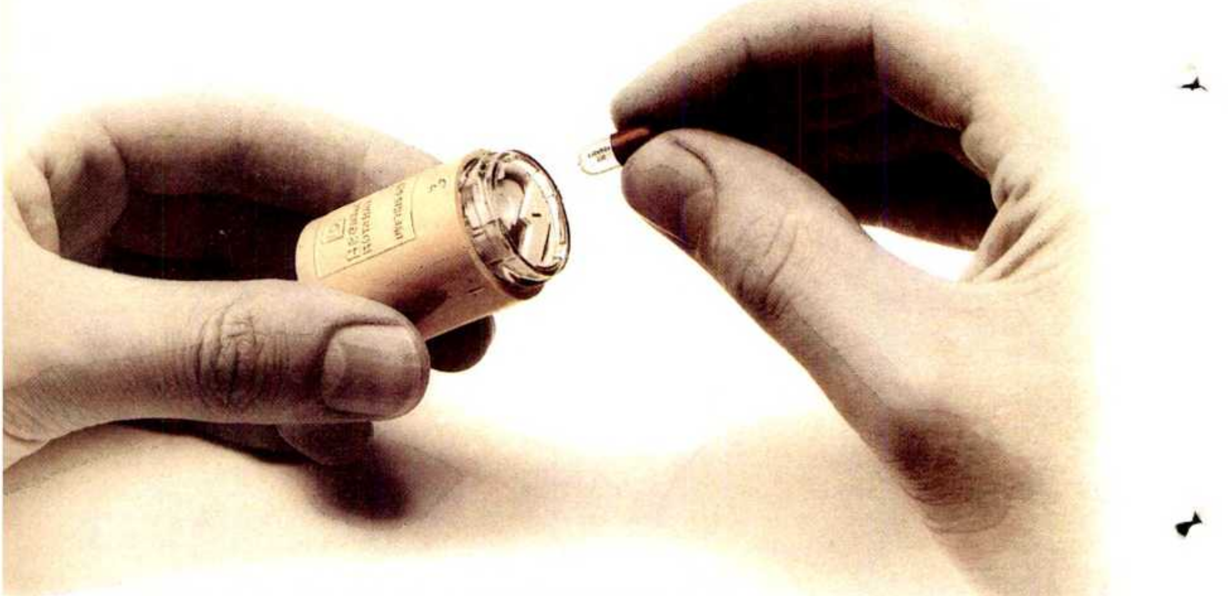

r use in conjunction with the Becotide Rotahaler as a
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A GREATER DEGREE OF CERTAINTY – A

COTIDE ROTACAPS PRESCRIBING INFORMATION

SENTATION

otide Rotacaps, an alternative inhalation form of beclomethasone dipropionate to otide Inhaler, are especially valuable for treating patients who are unable to use surised inhalers effectively or who might use them incorrectly.
otide Rotacaps contain a mixture of microfine beclomethasone dipropionate BP larger particle lactose in buff or chocolate-brown/colourless hard gelatine idges. Each Becotide Rotacap contains 100 micrograms (buff) or 200 micrograms colate-brown) of beclomethasone dipropionate BP and is marked Becotide 100 ecotide 200. The contents of a Rotacap are inhaled using a specially developed ce called a Rotahaler which cuts the cartridge into two halves that rotate and ase the drug when the patient inhales. This breath actuation is very sensitive and e drug is fully available even at the lowest inspiratory rates.

ICATIONS

otide Rotacaps are indicated for a wide range of patients with bronchial asthma. se patients include: those whose asthma is becoming worse and the relief ided by bronchodilators is less effective; those who are inadequately controlled odium cromoglycate in addition to bronchodilators; those with severe asthma are dependent on systemic corticosteroids, or adrenocorticotrophic hormone TH) or its synthetic equivalent.
otide Rotacaps are particularly important for managing severe asthma in children

DOSAGE AND ADMINISTRATION

Becotide Rotacaps are for inhalation use only, using a Becotide Rotahaler. For optimum results Becotide Rotacaps should be used regularly.
Adults: One 200 micrograms Rotacap, three or four times a day is the usual maintenance dose.
Children: One 100 micrograms Rotacap two, three or four times a day, according to the response.

CONTRA-INDICATIONS

No specific contra-indications to Becotide Rotacaps are known, but special care is necessary in patients with active or quiescent pulmonary tuberculosis.

PRECAUTIONS

Patients should be instructed in the proper use of the Rotahaler to ensure that the drug reaches the target areas within the lungs. They should also be made aware that Becotide Rotacaps have to be used regularly for optimum benefit.
The maximum daily intake of beclomethasone dipropionate should not exceed 1mg; significant reduction of plasma cortisol levels has been reported in patients who received twice this amount.
Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.
If there is no response to therapy within a week in patients previously not treated with systemic steroids or ACTH then consideration should be given to the probability that excessive mucus in the bronchi has prevented the drug from penetrating to its site of

inhaled steroid therapy of asthma

ROTACAPS*

ge of patients with chronic asthma

Becotide Inhaler is well established for the treatment of chronic asthma where inflammatory changes within the lungs reduce the response to bronchodilators; and for many previously steroid-dependent patients in eliminating or greatly reducing their need for systemic steroids, particularly severely asthmatic children who would be at risk from systemic side effects such as stunting of growth.

However, there are patients who do not obtain maximum effectiveness from Becotide Inhaler, and the Rotacaps/Rotahaler System has been developed with them in mind providing –

Breath-actuated control – for children, and those elderly or arthritic patients who may find it easier and more reliable.

Avoidance of faulty inhaler technique – for those patients who cannot co-ordinate the action of breathing in with the activation of a pressurised aerosol.

A better guarantee of effectiveness – for patients in whom Becotide Inhaler has not provided the anticipated benefit probably because of inadequate delivery of drug.

Appropriate routine prophylaxis – a way of helping to ensure that Becotide is used routinely by those patients who might misunderstand its role.

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apparent ineffectiveness before the trial of a short course of systemic steroid in relatively high dosage has been given to control secretion of mucus and other inflammatory changes in the lungs.

When transferring patients to Becotide Rotacaps from systemic steroids, please refer to the detailed procedure described in the Data Sheet.

SIDE EFFECTS

No major side effects attributable to the use of recommended doses of Becotide Rotacaps have been reported. Candidiasis of the mouth and throat (thrush) occurs in some patients; patients with high blood levels of Candida precipitins, indicating a previous infection, are more likely to develop this complication. The condition usually responds to topical antifungal therapy without discontinuing treatment with Becotide Rotacaps.

PACKAGE QUANTITIES

Becotide Rotacaps 100 micrograms in containers of 100 – (PL 0045/0119)
Becotide Rotacaps 200 micrograms in containers of 100 – (PL 0045/0120)

Further information is available on request.

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Br. J. Dis. Chest (1979) *73*, 18

LATE DEATHS AFTER RESECTION FOR BRONCHIAL CARCINOMA

J. R. BELCHER AND M. REHAHN

The London Chest Hospital

Summary

1267 patients who underwent surgical treatment for bronchial carcinoma during the period 1949–70 have been studied. 304 underwent thoracotomy without further resection; 88% died within 12 months; the maximum survival was 56 months. Of the remaining 963 patients, 869 late deaths are recorded, and the causes of these have been studied.

The 5-year actuarial survival rate was 25.9%; the 10-year rate 15.3%; the 15-year rate 9.3%; and the 20-year rate 3.9%. 610 of the 869 deaths were due to bronchial carcinoma; 79 were due to respiratory disease; 57 to coronary disease; and 23 to other neoplasms.

The percentage of total deaths due to bronchial carcinoma declined with the passage of time. It was 86.5% during the first year; 79.2% during the next 4 years; 53.7% from 5 to 10 years; and 39.3% over 10 years.

The second commonest cause of death was respiratory disease, which tended to be related to the extent of resection. Compared with a population of the same age and sex structure, suffering the death rates of England and Wales during the period involved, these patients show a massive excess of deaths from bronchial carcinoma and a smaller excess from respiratory disease; and a considerable shortfall from coronary disease, other carcinomas, and all other causes.

A more favourable probability of survival was linked with lobectomy, squamous cell type and the younger age group. A less favourable probability was linked with pneumonectomy, adenocarcinoma and older age-groups. There was no significant difference due to sex.

After the first 2 years, with their heavy death rate, the chances of surviving to 10 years improved by about 15% each year.

INTRODUCTION

Very little has been written about the recorded causes of late death after surgery for bronchial carcinoma; nearly all the studies in this field have been concerned with survival rates. The London Chest Hospital and the Middlesex Hospital, where a large number of patients were treated surgically for bronchial carcinoma by one of us (J.R.B.), have excellent follow-up arrangements. Advantage has been taken of these facilities to investigate the recorded causes of late death in the hope that something might be discovered about the natural history of bronchial carcinoma, and that it might prove relevant to other forms of malignant disease.

The Patients

This study of patients operated on by one of us at the London Chest and Middlesex Hospitals between 1949 and 1970, and a group of patients who were operated on by his first assistants at these hospitals between the years 1950 and 1963. The results of surgery in the 1950–63 group has already been reported (Belcher & Anderson 1965). The follow-up period ended on 31 December 1972 and thus the minimum time elapsed since operation is 5 years.

The study excludes operative and hospital deaths. 1289 patients survived operation and entered the study. Of these, 22 have gone abroad or have otherwise been lost sight of, leaving 1267 for consideration (147 women and 1120 men). 76% of the patients presented for operation aged beween 51 and 70 years and 16% were aged between 41 and 50 years.

476 patients underwent lobectomy, 473 pneumonectomy, 304 had thoracotomy alone and 14 had other procedures.

94 patients were alive at the last follow-up date and 1173 were dead. For cause of death we have relied almost entirely on copies of the death certificates obtained from Somerset House. Over 60% of the patients died in hospital, the rest died in their own home. Few post mortems were performed. Where two causes were given on the death certificate e.g. (i) bronchial carcinoma, (ii) respiratory failure or (i) respiratory failure, (ii) bronchial carcinoma, the first cause listed has been used in the study.

RESULTS

Thoracotomy

304 (24%) of the 1267 patients underwent thoracotomy without resection. These were 34 women and 270 men. They are all now dead. The majority died within 12 months of operation; 29 survived 1 year but not 2 years; and 6 survived 2 or more years (maximum survival 56 months). The great majority died of bronchial carcinoma, and no further study has been made of them here.

Resection

963 patients (115 women, 848 men) survived resection, and these form the major part of our study. There have so far (1975) been 869 late deaths (100 women, 769 men). Table I shows the pattern of deaths.

Table I. Deaths after resection

Time elapsed after resection (years)	*Deaths*	*Survivors*	*Total*
Less than 1	371	—	371
1 and not 5	343	—	343
5 and not 10	92	33	125
10 or more	63	61	124
Total	869	94	963

During the period of the study, the cumulative numbers presenting for operation were as shown in Table II.

Ages were recorded by decades. The average (grouped) age at operation was 57 years. Age at operation rose slightly during the period of the study: in the 1950s it was 56, in the 1960s 58, and in 1970 it was 61 years. Fig. 1 shows an actuarial survival

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Table II. Cumulative numbers presenting for operation during the study

Year	*No. of patients*	*Minimum follow-up* (years)	*Cumulative total*
1949/50	40	25	40
1951/5	145	20	185
1956/60	327	15	512
1961/5	260	10	772
1966/70	191	5	963

curve, calculated on an annual basis. After the first 2 years the probability of annual survival is fairly constant. Table III shows the cumulative probabilities of survival (as shown in Fig. 1) for selected periods.

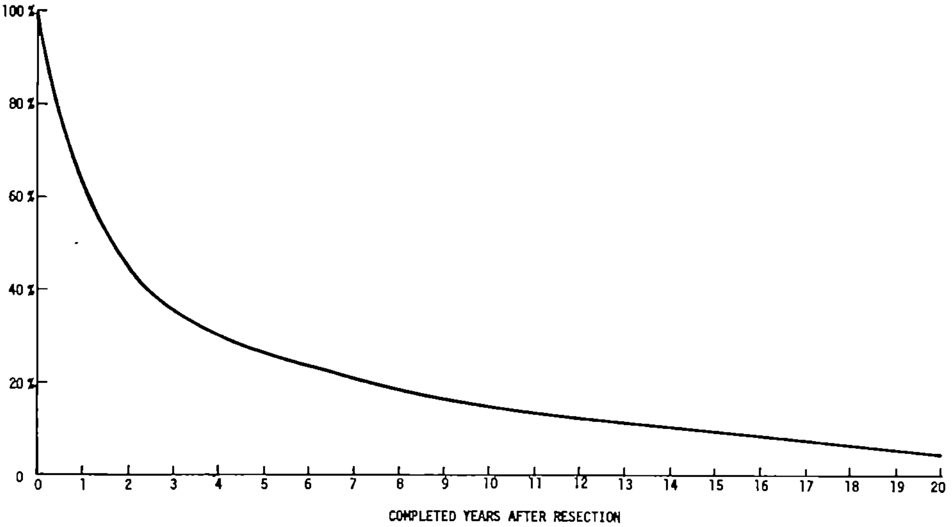

Fig. 1. Cumulative survival after resection

Table III. Cumulative probability of survival

Survival (years)	*P*
1	0.61
2	0.45
3	0.35
4	0.29
5	0.26
10	0.15
15	0.09
15	0.09
20	0.04

The majority of patients were aged between 41–70 years. As death rates in the population at large start to increase sharply after 40 years of age, separate survival curves have been calculated for the three age groups 41–50, 51–60, and 61–70 in the study. These are shown as Fig. 2. The irregular nature of the curves after 10 years is due to the small numbers involved. The curves for 41–50 years and 51–60 years are indistinguishable; that for the 61–70 years age-group falls below. The probabilities of survival for 5 years and 10 years exactly are shown in Table IV.

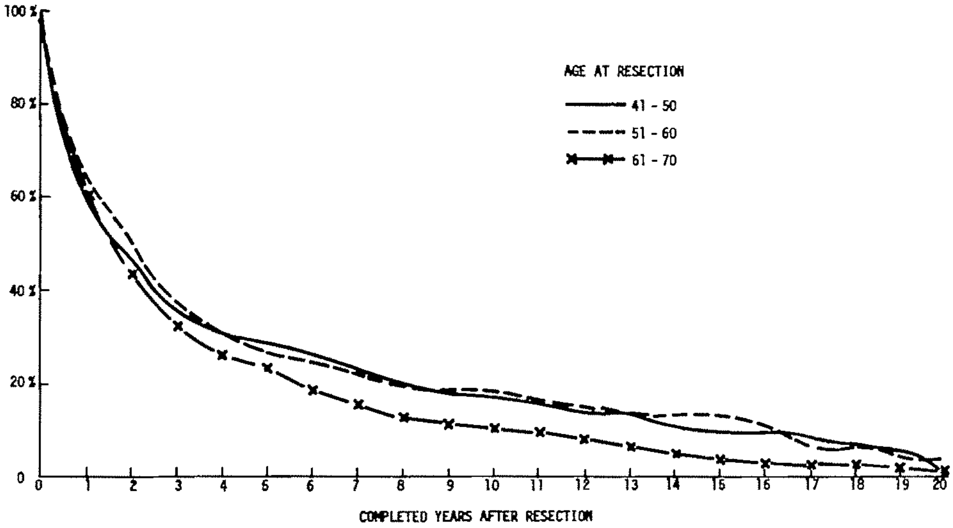

Fig. 2. Survival after resection according to age group

The combined curves for 41–50 and 51–60 are significantly higher than that for 61–70: at 5 years, $P < 0.01$, at 10 years, $P < 0.005$ and at 15 years $P < 0.001$. In other words, the lower probabilities for the older group become more marked as time goes by, which is in accord with common sense.

Causes of late deaths

Out of the total of 869 late deaths, the cause is unknown in 73 cases. Most of these deaths occurred in the early stage (1950–5) of the study, when the organization for obtain-

Table IV. Probability of survival according to age

Survival (years)	*P* 41–50 years	 51–60 years	 61–70 years
1	0.29	0.27	0.24
5	0.17	0.18	0.11
10	0.09	0.13	0.04

P, 25,436

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ing copies of death certificates was not as good as it is now. The certified causes of late death are shown in Table V.

Splitting these late deaths in terms of survival produces Table VI, which clearly shows the reduction in the percentage of deaths due to bronchial carcinoma as time of survival increases. This decrease is statistically very highly significant ($P < 0.001$).

Now examining in detail the numbers and percentages of deaths from causes other than bronchial carcinoma, as shown in Table VII below, there are highly significant differences between the total numbers in each classification ($P < 0.001$), but the fluctuations with time of survival are not significant.

Table V. Certified causes of late deaths

Cause of death	*No. of cases*	*% of known causes*	*% of known causes other than bronchial carcinoma**
Bronchial carcinoma	610	77	
Respiratory disease	79	10	42
Coronary disease	57	7	31
Other neoplasms	23	3	12
Other	27	3	15
Total	769		

* 186 cases.

Table VI. Causes of late deaths according to time of survival

Survival (years)	*Bronchial carcinoma*	*Other causes*	*Total deaths*
Less than 1	294 (86%)	46 (14%)	340
1 and not 5	247 (79%)	65 (21%)	312
5 and not 10	47 (53%)	41 (47%)	88
10 or more	22 (39%)	34 (61%)	56
Total	610	186	796

Table VII. Causes of late deaths (other than bronchial cardinoma) according to time of survival

Survival (years)	*Respiratory disease*	*Coronary disease*	*Other neoplasms*	*Other causes*	*Total deaths*
Less than 1	24 (52%)	8 (17%)	3 (6%)	11 (24%)	46
1 and not 5	25 (38%)	18 (27%)	10 (15%)	12 (18%)	65
5 and not 10	19 (46%)	18 (44%)	3 (7%)	1 (2%)	41
More than 10	11 (32%)	13 (38%)	7 (21%)	3 (9%)	34
Total	79	57	23	27	186

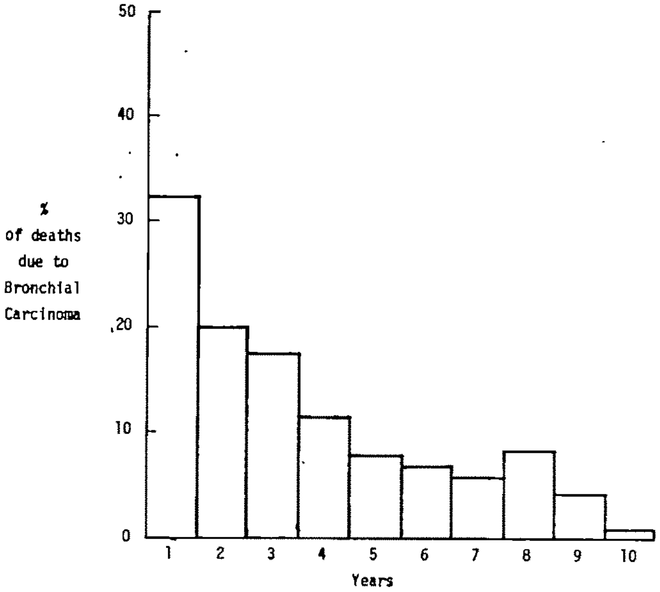

Fig. 3. Deaths from bronchial carcinoma in each year for the first 10 years of follow-up

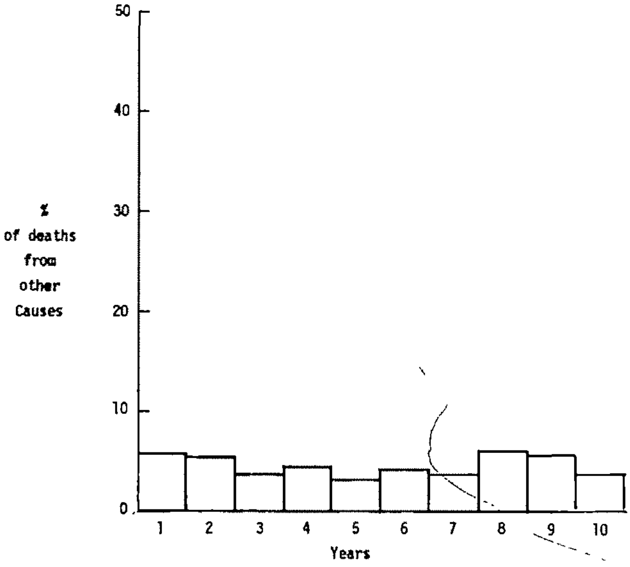

Fig. 4. Deaths from all other causes in each year for the first 10 years of follow-up

Pattern of late deaths

The pattern of late deaths has been studied using actuarial methods. Fig. 3 shows the percentage of deaths in each year from bronchial carcinoma for the first 10 years of follow-up; Fig. 4 shows the percentage of deaths from all other recorded causes. Bronchial carcinoma shows a negative exponential pattern, while 'all other known causes' is more-or-less linear and averages 4.65% per annum during the first 10 years.

Fig. 5 develops this information into survival curves, showing 'survival' (i.e. actual survival or death from other recorded cause) for bronchial carcinoma, and 'survival' for all other recorded causes. The bronchial carcinoma curve is negative exponential, and the 'other causes' is linear. (The appropriate equations have been fitted to the data of Fig. 3 and found to be very highly significant.)

The probabilities of survival therefore increase markedly as time passes. Using the data for the total 869 late deaths from any cause, Table VIII shows the increase in probability of reaching 5 years and 10 years at various time-points. Expressed in a different way, the

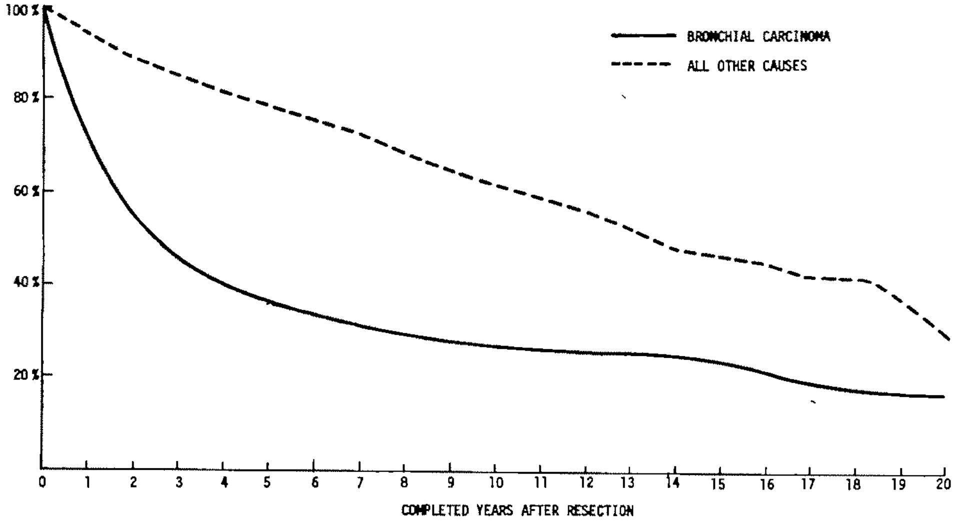

Fig. 5. Survival curves for bronchial carcinoma and all other causes of death

Table VIII. Probability of 5- and 10-year survival at various times

Time	*P*	
	Survival to 5 years	Survival to 10 years
After resection	0.26	0.15
At 1 year	0.42	0.25
At 2 years	0.58	0.34
At 3 years	0.74	0.44
At 4 years	0.89	0.52
At 5 years		0.58
At 6 years		0.67
At 7 years		0.73
At 8 years		0.86
At 9 years		0.95

chance of surviving to 5 years increases approximately 15 percentage points and the chance of surviving 10 years approximately 9 percentage points per year.

Comparison with deaths in the general populations

In the period of the study 1950–72 there was a slight decrease in the national death rate from all causes in England and Wales, but marked increase in rates for two particular causes of death for both sexes, bronchial carcinoma and coronary heart disease.

The 'population' of this study is recorded by age in decades, i.e. 21–30, 31–40, etc., and it is very different in both age structure and sex ratio from the population of England and Wales as a whole. Death rates for England and Wales are given in the Statistical Reviews of the Registrar General by decades, i.e. 25–34, 35–44, etc., which straddle the age-groups of the study. The death rates published for, say, 25–34 can be taken as an approximation to an average death rate for the 21–30-year-old group for a period of 10 years.

The death rates for England and Wales for all causes for bronchial carcinoma and for the other causes considered in this study have been standardized by reference to the age and sex structure of the 'population' in the study. A simple average has been taken of the rates at 5-yearly intervals for the years from 1950 to 1975.

These standardized and averaged rates have been applied to the starting population of 963 patients; expected deaths have been calculated for the first 5 years, and then for the second 5 years taking due heed of patients with only partial completion of this interval. The expected numbers of deaths by cause thus obtained are shown in Table IX.

Table IX. Expected and observed numbers of deaths

Cause	*First 5 years*	*Second 5 years*	*Expected 10 years*	*Observed 10 years*
Bronchial carcinoma	13	10	23	588
Respiratory disease	23	18	41	68
Coronary disease	42	33	73	44
Other neoplasms	21	19	41	16
Other	52	43	95	24
Total	151	123	274	740

There is a massive excess for bronchial carcinoma and a smaller excess for respiratory disease. Coronary disease, other cancers and other causes, however, are well below expectation.

The relatively low incidence of deaths from ischaemic heart disease is surprising. With a common aetiological factor (cigarette smoking) it might have been expected that it would be above normal in patients with bronchial carcinoma. It is possible that this lower incidence is because over 70% of patients give up smoking after surgery for bronchial carcinoma, and the incidence of coronary thrombosis is said to fall in these circumstances. The lower incidence of other carcinomas is interesting; could it be that the immune system which allows patients to survive for long periods after operation for bronchial carcinoma also militates against the development of other cancers? It remains very difficult to explain the very low proportion of deaths from other causes.

Influence of cell type

The cell type was recorded for 914 of the 963 patients in the study. There were 553 squamous (60%); 215 undifferentiated or oat-cell (24%) and 146 adenocarcinomas (16%). Actuarial survival probabilities have been calculated at intervals and Table X shows the results. At 5 years exactly, there is no significant difference between squamous and undifferentiated tumours, but both are better than adenocarcinoma ($P < 0.001$ and 0.05 respectively). At 10 years exactly squamous is better than adenocarcinoma ($P < 0.025$), but there is no significant difference between other pairings. At later points squamous remains higher than the other two types, but the difference is not statistically significant. It is clear from these comparisons that the squamous is the least aggressive and the adenocarcinoma the most aggressive. (The small oat-cell group has been included amongst the undifferentiated tumours.)

Table X. Probability of survival according to cell type

Survival (years)	P		
	Squamous	Undiff. or oat-cell	Adeno
1	0.68	0.53	0.54
5	0.29	0.25	0.17
10	0.18	0.14	0.11
15	0.12	0.07	0.05
20	0.06	0.04	0.02

Late deaths in women

115 women survived resection, of whom 25 survived at least 5 years and 14 at least 10 years. The survival curves for men and women for the first 10 years are indistinguishable.

The average grouped age at operation for women was 55 years which is significantly lower ($P < 0.01$) than that of 58 years for men. This is due to relatively more women in the 41–50 years age-group and relatively fewer in the 61–70 years age-group. The causes of late death in women are shown in Table XI.

Table XI. Causes of late deaths in women

Cause of death	*No. of cases*	*% of known causes*	*% of known causes other than bronchial carcinoma**
Bronchial carcinoma	79	81	
Respiratory disease	6	6	32
Coronary disease	2	2	10
Other neoplasms	4	4	21
Other	7	7	37
Total	98		

* 19 cases

The overwhelming recorded cause of late death in women was bronchial carcinoma, as for the men. Proportionately fewer deaths were recorded from respiratory failure and from coronary disease for women than for men, and correspondingly more deaths from other neoplasms and all other causes. The two cases of coronary thrombosis were in women aged 51–60 and 61–70 at operation, who survived 1 year and 5 years respectively. Table XII shows the decline, as for the men, in the proportion of deaths from bronchial carcinoma with the passage of survival time.

Table XII. Causes of late deaths in women according to time of survival

Survival (years)	*Bronchial carcinoma*	*Other causes*	*Total deaths*
1	34 (92%)	3 (8%)	37
1–5	37 (70%)	16 (30%)	53
5 years	8 (68%)	4 (33%)	12

Late deaths from other neoplasms

There were 23 late deaths from carcinoma other than those of the bronchus: stomach 5, larynx 4, oesophagus 3, colon 3, sarcoma 2, pancreas 2, and breast, bladder, ileum and myeloma 1 each. Four of these cancers caused death within 12 months, 5 more within the second year, and another five within the third, fourth and fifth years. Two more patients survived 5 but not 10 years, 6 survived 10 but not 15 years, and the final patient survived just over 18 years.

Using the standardized and averaged death rates discussed above, the comparison shown in Table XIII may be made. During the early years of follow-up, therefore, the deaths from other carcinoma were in line with expectation; later, they were swamped—as for coronary disease and other causes—by the excess deaths from bronchial carcinoma.

Table XIII. Expected and observed deaths from other neoplasms

Survival (years)	*Observed*	*Expected*
Less than 2	9	9
2 and not 5	5	13
5 and not 10	2	18

The figures do demonstrate the recognized association of laryngeal and bronchial carcinomas. For the population of the study, about 1.5% of deaths from all carcinomas except bronchial would be expected to be caused by laryngeal carcinoma; whereas 1 death actually occurred in the first 2 years, and 3 deaths in the later years of follow-up.

Deaths from all other causes

There were 27 deaths certified as due to causes other than bronchial or other carcinoma, respiratory disease or coronary disease.

A small group of deaths occurred very soon after discharge from the hospital and were attributable to the operation, being due to empyema, bronchopleural fistula, and pulmonary emboli.

There were 8 late deaths attributed to cerebrovascular accidents. Normally many more would be expected from a population of this sex and age—10 in the first 5 years of follow-up—but it would appear that this cause, like all the other non-respiratory causes, has been swamped by the gross excess of bronchial carcinomas.

Influence of type of resection

476 patients underwent lobectomy and 473 pneumonectomy. Actuarial survival rates have been calculated at intervals for each group and the results are in Table XIV. The patients therefore had a better survival rate after lobectomy than after pneumonectomy throughout the 20 years. Looking at the principal causes of death, Table XV has been produced.

Table XV. Probability of survival according to type of resection

Survival (years)	*P*		*P of difference* (1-tail)
	Lobectomy	Pneumonectomy	
1	0.68	0.57	0.001
5	0.30	0.22	0.025
10	0.18	0.13	0.050
15	0.11	0.08	N.S.
20	0.06	0.04	N.S.

Table XV. Principal causes of death according to type of resection

Survival (years)	*Lobectomy* ($n=419$)			*Pneumonectomy* ($n=434$)		
	Bronchial carcinoma	Respiratory disease	Other	Bronchial carcinoma	Respiratory disease	Other
1	132	9	13	155	15	40
1 and not 5	131	11	39	113	14	31
5 and not 10	29	9	14	17	10	12
10 and not 15	5	4	13	7	3	9
15 and not 20	6	—	4	3	3	2
Total	303 (72%)	33 (8%)	83 (20%)	295 (68%)	45 (10%)	94 (22%)

During the first year 154 patients died after lobectomy: 132 (87%) from bronchial carcinoma and 9 (6%) from other respiratory disease (total 93%). 210 patients died after pneumonectomy, 155 (74%) from bronchial carcinoma and 15 (71%) from respiratory disease (total 81%). These differences, both of deaths from bronchial carcinoma and all deaths from lung disease, are statistically very highly significant ($P < 0.001$). After this first year, while difference exist, they are not statistically significant; nor are the proportions of the total deaths significantly different.

DISCUSSION

Almost all the information about cause of death has been derived from death certificates. The validity of the certification must be considered. It might be argued that once a patient was known to have a bronchial carcinoma this would be likely to be given as the cause of death. The mode of death from such causes as coronary thrombosis and cerebrovascular accident, however, makes it unlikely that such deaths would be erroneously certified as death from bronchial carcinoma. On the other hand where death is certified as due to bronchopneumonia or respiratory failure—and more particularly where these are given in conjunction with bronchial carcinoma—difficulties do arise. We have dealt with this in what seems the only possible way, by taking the primary cause of death as quoted and by quoting the figures for respiratory failure (where this is the primary cause) separately.

A surprising finding was that the proportion of deaths due to bronchial carcinoma amongst the patients at risk fell year-by-year exponentially. It had been thought that the large number of deaths known to occur within 2 years of resection was due to undetected secondaries, and that therefore the early steep fall in the proportion of survivors would be succeeded by a linear reduction.

Bloom et al. (1962) observed that the deaths amongst patients with untreated carcinoma of the breast was exponential up to 10 years, and this finding is common amongst other forms of malignant disease. However, as it is certain that metastases are already present in many patients at the time of their resection for bronchial carcinoma, the fact that the exponential pattern starts immediately after resection suggests that the removal of the tumour must have some effect on the host's ability to deal with these metastases. This supports the policy of Smith (1957) who has for so many years advocated an aggressive approach to the surgical treatment of bronchial carcinoma.

Five earlier publications have been found which refer specifically to the causes of late deaths after resection for bronchial carcinoma. Smith (1970) reports 38 such deaths between 5 and 10 years after resection, of which 20 (53%) were due to bronchial carcinoma, the numbers falling off each year. In that series also, respiratory failure was the second commonest cause of death; 3 died from coronary thrombosis and 4 from other cancers. These figures are similar to the series reported here, and they were based not on the reports from the Registrar General, but on information obtained by the surgeon himself. Ashor et al. (1975) reported a 27% 5-year survival rate and a 18% 10-year survival rate; they showed that there was little difference in the prognosis of the different cell types (except the oat-cell variety) for 5- and 10-year survival, as was the case in this patient reported here. Watson's figures (1968) are also very similar to the series reported here in that 52% of the deaths between 5 and 10 years, and 35% after that time, were due to bronchial carcinoma.

Again, LeRoux's figures (1968) are similar to those reported in this paper. Of the survivors of pneumonectomy, 47% were dead from bronchial carcinoma within 2 years of resection and the second commonest causes of late death were respiratory infection and congestive heart failure. Twenty-nine of the 77 late deaths due to causes other than bronchial carcinoma were due to coronary disease (37%). The comparable figure in this series is 31%.

On the other hand Shields and Robinette (1973) reported very few recurrent tumours or new primaries in group of 212 deaths occurring more than 5 years after resection (only 5%) and all of these occurred within the sixth year of follow-up. Another 8% were recorded as having second primaries, but even so those two groups together total only 13%, which is startlingly different from the 48% found here. It is very difficult to account for this difference, as both series are large, both were collected over similar periods and both have good follow-up records. On the other hand, the proportion dying of new primaries in other organs is 15%, almost exactly the same as that reported here (14%).

In this series, it has been shown that a rather better probability of survival was linked, individually, with lobectomy, squamous cell type and the younger age-group. The conjunction of these factors has been examined in case, for example, the apparent favourable effect of squamous cells merely reflected the higher incidence of such in the lower age-groups. For type of resection versus age, a slight excess of lobectomies were found in the older patients and a corresponding shortfall in the younger, though the differences were not statistically significant. For resection versus cell type, a very highly significant difference ($P<0.001$) was found: there was an excess of the less aggressive squamous cells amongst the patients who had pneumonectomies and a shortfall of the adenocarcinomas, and the reverse for the lobectomies. For cell type versus age at operation, there was again a highly significant difference ($P<0.001$), with an excess of the more aggressive adenocarcinomas observed in the 41–50 years age-group. Thus there was no linking of the three favourable factors: in fact, out of the 888 patients in the 41–70 years age range, only 34 were between 41 and 50 years, underwent lobectomy and had a squamous cell carcinoma. Lastly, unlike the incidence of deaths due to other carcinomas, bronchial carcinoma continued to cause deaths at a high rate both in relation to deaths in the series from other causes and in relation to death rates in the population at large (standardized for age and sex). This adds weight to the widely held conviction that it is never wise to claim that a cancer has been 'cured'.

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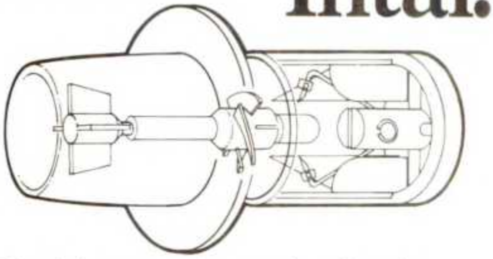

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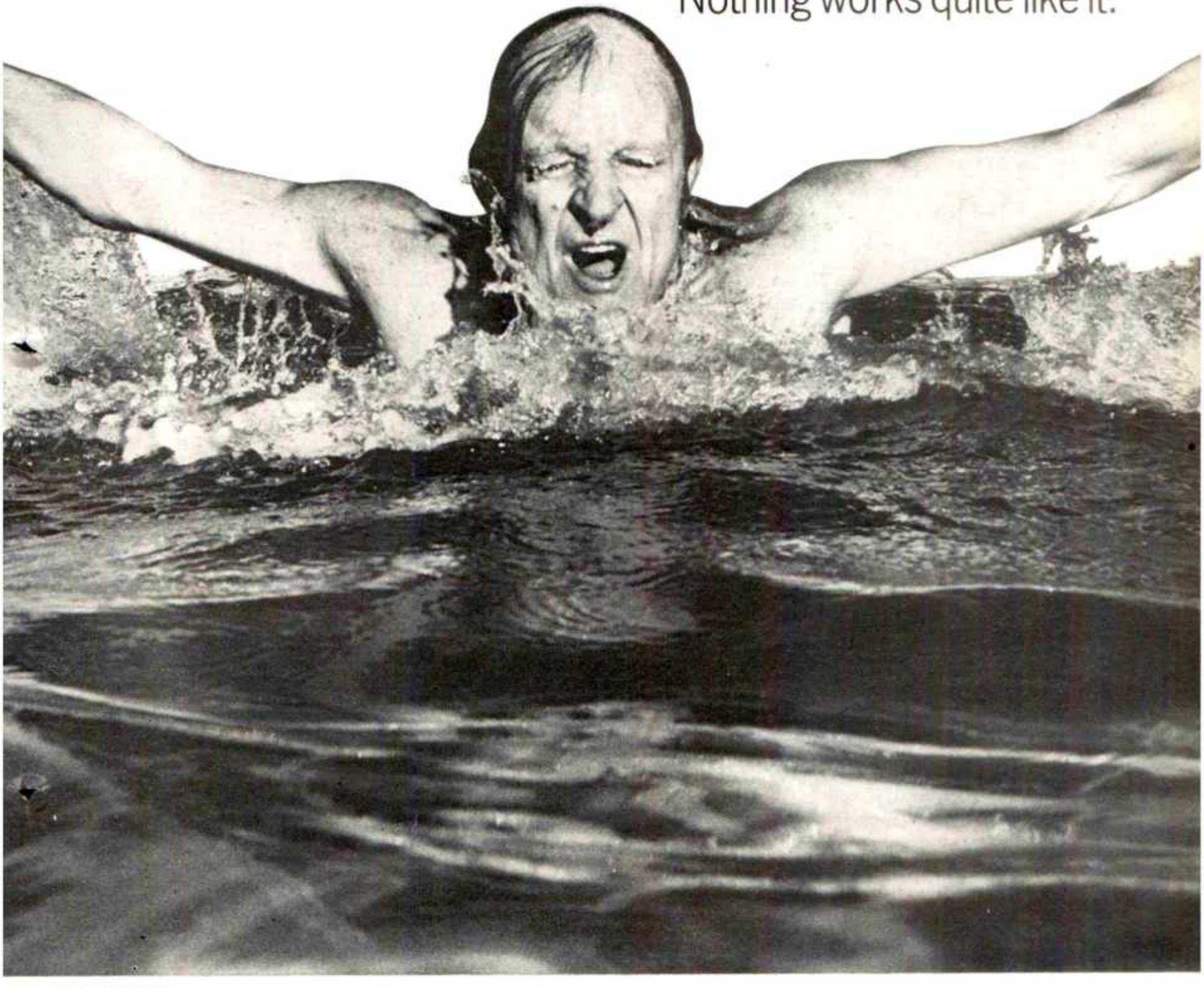

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LEGIONNAIRES' DISEASE: A CLINICAL DESCRIPTION OF THIRTEEN CASES

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Summary

We describe 13 patients with legionnaires' disease in Nottingham, all presenting with lobar pneumonia. Six patients required artificial ventilation and 2 died. No common source of infection has yet been identified, but the disease appears to be prevalent and possibly endemic in this city.

Introduction

An explosive outbreak of pneumonia among people who had attended an American Legion convention in Philadelphia in 1976 (Fraser et al. 1977) subsequently led to the isolation of a new respiratory pathogen. The staining and growth characteristics of the organism, methods for its identification in post-mortem lung tissue and serological techniques for confirming infection have also been described (Chandler et al. 1977; McDade et al. 1977). The Philadelphia outbreak suggested that there was an unidentified source of infection within the convention hotel.

Since the Philadelphia outbreak the same organism has been implicated in previous outbreaks of severe pneumonia, one at a large psychiatric hospital in Washington, D.C., in 1965 (Morbidity and Mortality Weekly Report 1965) and another in people returning from a holiday in Spain in 1973 (Lawson et al. 1977). One hundred and fifty sporadic cases have also been confirmed in the USA (Morbidity and Mortality Weekly Report 1977) and to date 32 cases have been identified in England and Wales (Bartlett, C., personal communication), some of which have already been reported in short letters (Ashford et al. 1977; Lees et al. 1977). Twelve cases have been admitted to the two main hospitals in Nottingham since June 1977 and an earlier fatal case has also been confirmed. A preliminary report on some of these has already appeared (Macrae & Lewis 1977). The clinical presentation of these cases was remarkably uniform, although of varying severity. The occurrence of 13 apparently unconnected cases over several months in a small area is so far unique, contrasting with the earlier explosive outbreaks over very limited periods of time and also with the low incidence of subsequent sporadic cases in widely scattered geographical areas.

Patients and Methods

Clinical diagnosis

During a 7-week period in August to September 1977, 7 patients were admitted to the City Hospital Nottingham, with lobar pneumonia; all required assisted ventilation and 4 died. This led to the suspicion of legionnaires' disease, which was later confirmed in 4. Of the other 3, 2 were staphylococcal and 1 is unexplained. Eight other patients admitted between May 1977 and February 1978 were subsequently also shown to have legionnaires' disease, as was another who died in 1976 and who was investigated retrospectively because of unusual organisms in post-mortem lung tissue.

Microbiological investigations

The following investigations were performed in all cases:

1. Sputum and blood culture for bacterial pathogens.
2. Culture of sputum and throat swabs for viruses.
3. Antibody titres on sera, usually paired, for virus, mycoplasma, chlamydia and coxiella infections.
4. Immunofluorescent tests on these sera and on post-mortem lung tissue performed at the Centre for Disease Control, Atlanta, and more recently by the Public Health Laboratory Service, Nottingham.

Any one of the following criteria was accepted as evidence for legionnaires' disease (McDade et al. 1977; Bartlett, C., personal communication):

1. A four-fold or greater rise in specific antibody titre.
2. A single titre of at least 1 in 256.
3. Demonstration of organisms in lung tissue by immunofluorescent staining.

RESULTS

Clinical description

The mean age of the 13 patients, 4 of whom were women, was 47 (Table I). All but 2 smoked between 10 and 60 cigarettes daily and 4 were chronic bronchitics. Eleven of the patients had a very similar clinical picture although varying in severity. They presented with a 5–10-day history of malaise. Common symptoms were increasing breathlessness (9), cough (7), pleuritic chest pain (5), confusion (5), severe abdominal pain (4) and diarrhoea preceding any antibiotic therapy (3). Indeed, 2 of the mildest cases presented with abdominal pain and vomiting but without chest symptoms and a third was admitted because of a gastrointestinal haemorrhage. The twelfth case presented with headache, vomiting, photophobia and neck stiffness, with normal cerebrospinal fluid. Sputum production was not a prominent feature before admission except in the chronic bronchitics.

On admission all patients had signs of lobar pneumonia with localized coarse crackles (9), bronchial breathing (7) and, in 2 patients, a friction rub. All were pyrexial (38–40°C) with tachycardia (100–140/min), tachypnoea (20–50/min) and, in the 7 where it was tested, postural hypotension and lowered venous pressure. Five patients were very confused, and 1 had papilloedema but no other neurological signs. One patient had palmar erythema and spider naevi associated with abnormal liver function tests; all these abnormalities disappeared before discharge.

The thirteenth case, who presented in June 1976, was under treatment with high doses of prednisolone and cyclophosphamide for systemic lupus erythematosus, which was still active. Her presentation was atypical in that she was symptom-free until the day before admission when she became pyrexial with pleuritic chest pain. She had minimal chest signs but deteriorated very rapidly both clinically and radiologically, dying 4 days after the onset of her symptoms.

Table I. Clinical details of the 13 cases

Case	*Age*	*Admitted*	*Consolidation on X-ray*		*Antibiotic*	*Assisted ventilation*	*Outcome**	*Legionnaires' titre**
			Admission	Spread				
1	42	16 June 76	RLL	LLL	Ampicillin + flucloxacillin Doxycycline	No	Died (3)	Lung tissue
2	39	8 May 77	LLL	LUL + RUL	Ampicillin + benzylpenicillin Flucloxacillin + gentamicin Chloramphenicol	4 days	Home (47)	64 (22) 256 (220)
3	61	22 June 77	LLL	RML	Ampicillin + cloxacillin Tetracycline	No	Home (14)	128 (15) 512 (21)
4	31	11 Aug 77	RLL	—	Tetracycline Ampicillin + cloxacillin	No	Home (11)	<32 (4) 512 (14)
5	32	16 Aug 77	RML	RLL + LLL	Benzylpenicillin Flucloxacillin + gentamicin	5 days	Home (17)	32 (5) 512 (58)
6	41	18 Aug 77	RLL	RUL	Ampicillin + flucloxacillin Gentamicin	4 days	Home (27)	1024 (69)
7	63	31 Aug 77	L lung	RLL	Ampicillin + cloxacillin Gentamicin Chloramphenicol	7 days	Died (9)	128 (5) + lung
8	66	12 Sept 77	RLL	—	Ampicillin Tetracycline	No	Home (10)	1024 (123)
9	52	18 Sept 77	RUL + RLL	LLL	Ampicillin + cloxacillin Chloramphenicol + metronidazole Erythromycin Flucloxacillin + gentamicin	20 days	Home (51)	64 (7) 256 (22)
10	49	6 Oct 77	R lung	RUL	Erythromycin	4 days	Home (12)	128 (10) 256 (20)
11	57	27 Oct 77	LLL	—	Amoyxcillin	No	Home (10)	<32 (14) 512 (114)
12	48	23 Nov 77	LLL	—	Benzylpenicillin Erythromycin	No	Home (6)	32 (7) 1024 (50)
13	38	3 Feb 78	RLL	—	Benzylpenicillin + cloxacillin	No	Home (8)	1024 (62)

* Number of days after admission shown in parentheses.

Radiological findings

In all cases, radiographs on admission showed lobar consolidation. This was initially limited to one, usually lower, lobe in 10 patients. In spite of conventional therapy, however, in all but 5 cases there was extension within 2 days to other lobes of the same or opposite lung (Fig. 1). Cavitation and pleural effusions were not seen.

In the 11 survivors radiological consolidation persisted for at least 7 weeks and in 5 for

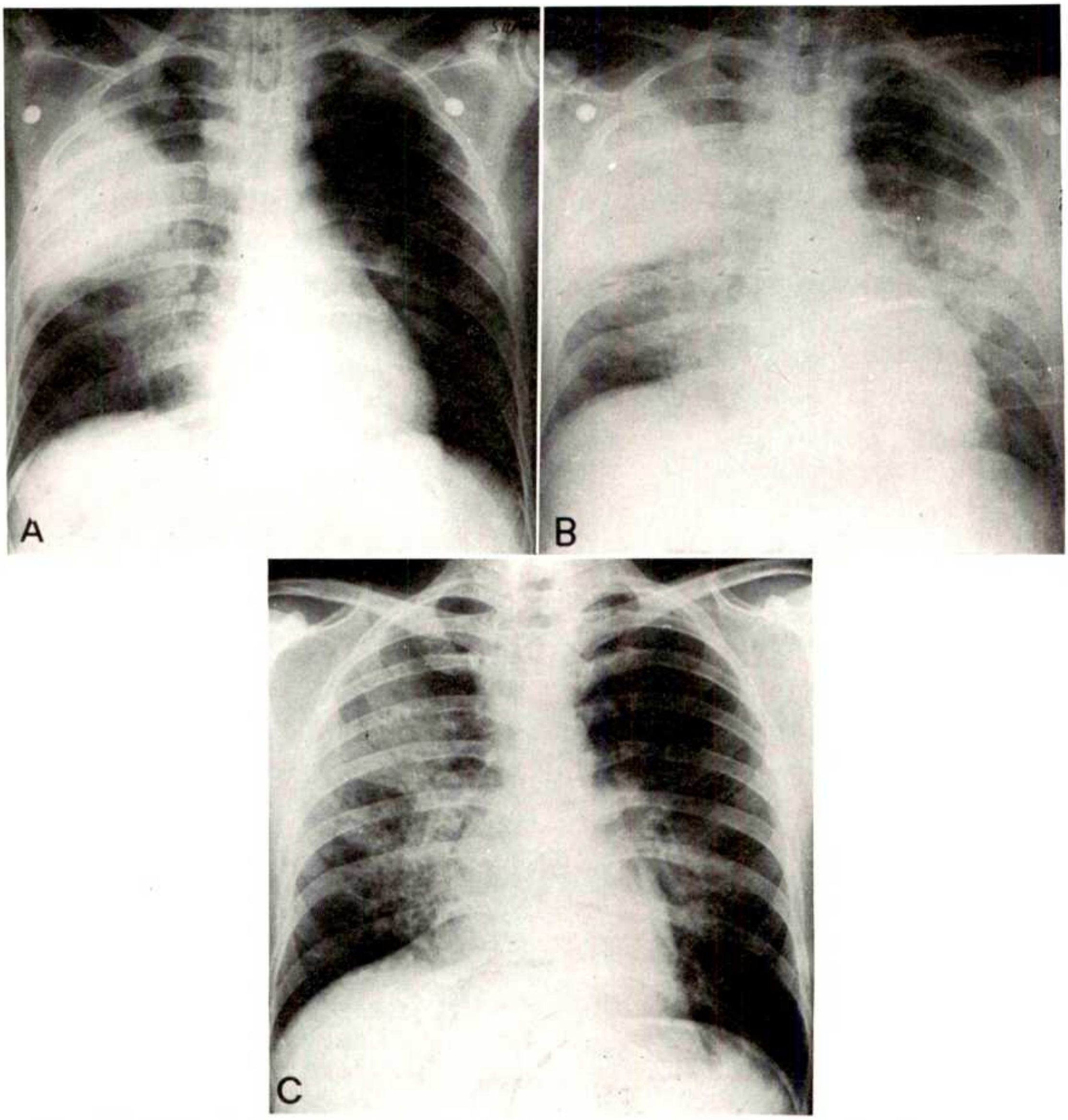

Fig. 1. Radiological changes in a severe case. A, Day after admission. B, 2 days later. C, After 10 days

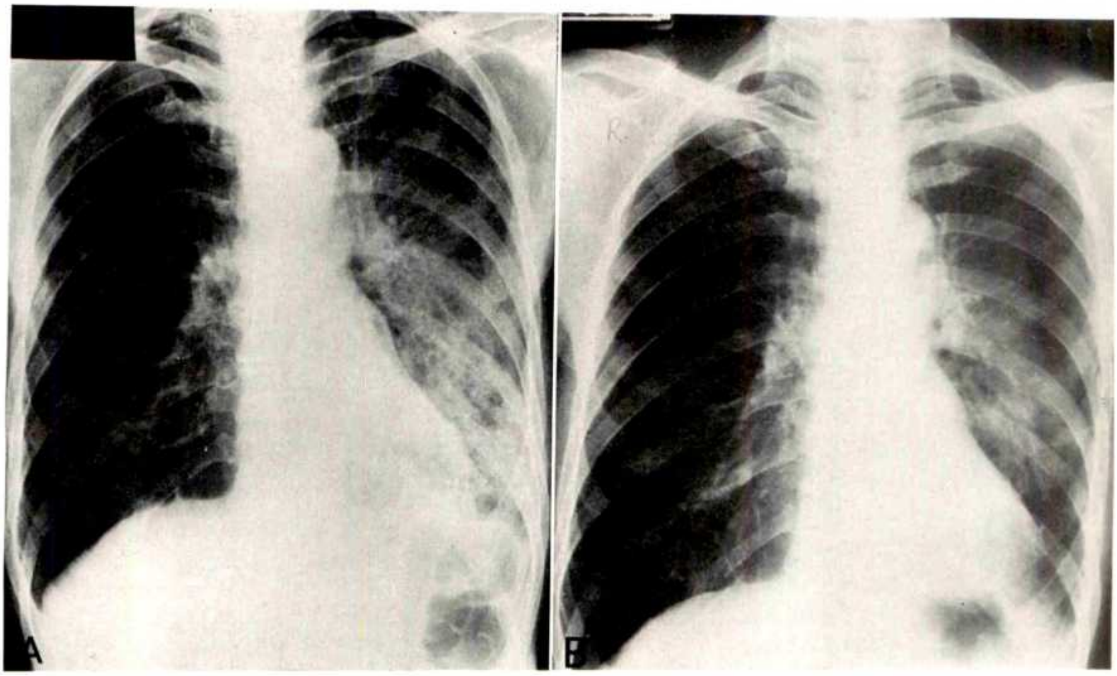

Fig. 2. Radiological changes in a mild case. A, Day of admission. B, 8 weeks later

14 weeks after the onset of the illness. Such a case is shown in Fig. 2; this patient was one of the less severe cases and was bronchoscoped because of the persisting consolidation to exclude a neoplasm.

Laboratory results

Eight patients had lymphopenia (200–1100 × 10^6/litre) irrespective of the neutrophil count (5100–14 200 × 10^6/litre). A high ESR (57–116 mm/hour) was invariable. Hypoalbuminaemia (17–24 g/litre) was present in the 5 patients in whom it was sought. Hyponatraemia (124–128 mmol/litre) was present in 7 and persisted after rehydration and mild uraemia (10–16 mmol/litre) was noted in 9 patients. These abnormalities were not related to the degree of severity on admission nor to the final outcome.

Six patients had arterial blood gas measurements on admission. All were hypoxic ($P\text{ao}_2$ 5.0–8.7 kPa, 40–65 mmHg) but not hypercapnic ($P\text{aco}_2$ 3.1–5.9 kPa, 25–45 mmHg).

Microbiological results

Pathogenic organisms (*Str. pneumoniae* and *Haemophilus influenzae*) were isolated from sputum in only 2 patients, both chronic bronchitics who did not respond to conventional therapy. Otherwise no evidence of bacterial, viral or other infections could be found until tests for legionnaires' disease were performed (Table I).

Treatment and progress

Seven of the patients had recieved antibiotics, mainly penicillin derivatives, before admission. Subsequent antibiotics were given in the order summarized in the table, usually intravenously. One patient was given erythromycin in the first instance because of suspected penicillin allergy. Despite rehydration, physiotherapy and administration of humidified oxygen 8 of the patients deteriorated clinically and radiologically. Six required intermittent positive-pressure ventilation (IPPV) for periods varying from 4 to 20 days because of progressive hypercapnia and hypoxia associated with drowsiness and sputum retention; all but one of these survived. Two patients developed marked deterioration in renal function, one requiring peritoneal dialysis for 2 weeks, with eventual complete recovery.

Follow-up

The 11 survivors were in hospital for periods varying from 6 days to 8 weeks and after discharge all complained of malaise and lethargy for several weeks and in one case for 3 months. Subsequent radiological findings have been described above. Most of the survivors could remember none of the events between admission and the following 4–7 days. This includes most who gave a full and coherent history on admission and whose illness was not severe enough to require IPPV.

Epidemiology

All patients lived in densely populated areas, all but 1 within an area of 12 square miles containing 160 000 people. The rest of our catchment area for acute medical admissions contains a population of 560 000 in further 670 square miles.

Two of the patients had visited the hotel implicated in the Benidorm outbreak, although at a different time and more than a year before admission. The suggested incubation period for legionnaires' disease is between 2 and 26 days (Fraser et al. 1977).

Other cases of lobar pneumonia

Three other cases of fatal pneumonia were admitted in August and September 1977 when the first 4 cases of legionnaires' disease were diagnosed. Two were found to have staphylococcal pneumonia and the cause was not established in the third. They resembled the severe cases of legionnaires' disease in their presentation, radiological, haematological and biochemical changes, and in requiring IPPV, yet no evidence of legionnaires' disease was found on examination of sera or post-mortem lung tissue. Thus legionnaires' disease may be indistinguishable from other causes of severe pneumonia.

Discussion

Comparison with other reports

Our findings are similar to those of the larger series of cases from Philadelphia (Fraser et al. 1977); in that study several cases who had not been admitted to hospital were identified, but this was only 19% of those affected. This suggests that the disease is usually serious, and their mortality of 16% confirms this. Many of our cases have also been very ill, half requiring IPPV compared with 20% in the Philadelphia outbreak. We have as yet been unable to screen individuals in the community to discover whether a milder form of the disease exists. However, we have begun a retrospective study of the case notes of all patients admitted to our hospitals between May and October 1977 and taken blood for serological studies in those who complained of breathlessness, chest pain, cough, sputum or fever for which no diagnosis was made. Over 300 patients have been reviewed without discovering any additional case.

The major difference in our series is that all presented with lobar pneumonia. In the Philadelphia cases, on the other hand, radiological findings were 'patchy, interstitial infiltrates or areas of consolidation'. We have also noted bronchial breathing and friction rubs, not previously reported. Extension of consolidation was common in the American report, but we have also found that radiological resolution is very slow. Lymphopenia, hyponatraemia and hypoalbuminaemia were common findings, hitherto unrecorded. Another striking feature was retrograde amnesia in nearly all survivors.

The fatal case who presented in 1976 may have been atypical because of current treatment with immunosuppresive agents; 5 other such patients have been described (Bock et al. 1978).

Recognition and treatment

Unless the disease occurs in an epidemic outbreak clinical differentation from other causes of lobar pneumonia may be impossible. Since in the severely ill patient lung biopsy, which is only diagnostic in a small proportion of cases, is usually unjustified, confirmation can only be made retrospectively. The disease should be considered in a young patient, in previous good health, who presents with a non-cavitating pneumonia with no microbiological cause being found; suspicious features include gastrointestinal symptoms, rapid spread of infection to other lobes, persistence of radiological consolidation, and retrograde amnesia.

There is little evidence that antibiotic therapy is of significant benefit. In vitro studies and those in experimental animals have given conflicting results (Fraser et al. 1978), although it appears that erythromycin and rifampicin may be beneficial. The latter is best reserved for tuberculosis unless a confident diagnosis of legionnaires' disease can be made early. Erythromycin (and tetracycline, which is ineffective in experimental models) was associated with a lower mortality than other antibiotics in the Philadelphia cases, but the difference was not statistically significant. We suggest that if a patient with unexplained lobar pneumonia shows no improvement within 48 hours on a conventional antibiotic regimen, such as flucloxacillin plus benzylpenicillin or ampicillin, erythromycin should be added, since this is known to be effective against the majority of other pathogens that could be responsible for lobar pneumonia in a previously fit patient. However, if the patient is already seriously ill on admission, it is now our policy, if staphylococci cannot be demonstrated in sputum by Gram stain, to use benzylpenicillin plus erythromycin from the outset. In addition, IPPV with its greater ability to correct hypoxaemia and assist sputum extraction by humidification, physiotherapy and suction, may be life-saving.

Epidemiological aspects

Of the 32 cases of legionnaires' disease confirmed in England and Wales to date (April 1978) 41% have come from a small area in Nottingham. Our experience differs from that of other investigators. Thus it has not been possible to find any common factor linking the cases and there is no evidence of an explosive outbreak. Also the geographical clustering of cases in a relatively small area, yet spread over several months, is unusual and contrasts with other isolated cases widely separated both in time and place. The highest concentration of sporadic cases previously reported is only 32 in the whole state of Vermont (Morbidity and Mortality Weekly Report 1977).

Severe pneumonia of uncertain cause is not uncommon, and it is possible that legionnaires' disease is far more prevalent than has yet been recognized elsewhere. The disease may have been in the community for many years and it is likely that further cases will come to light with greater access to diagnostic tests.

ADDENDUM (*October 1978*)

Since the above report was prepared, we have admitted a further 6 patients with acute pneumonia due to legionnaire's disease and have identified another case who became infected this year while staying at the same Benidorm hotel that was implicated in the 1973 outbreak.

With one exception, who died within a few hours of admission of a myocardial infarct, all were previously healthy and made a complete recovery. Unlike our patients in the summer of 1977, they were only moderately ill, and none required IPPV. Based on our earlier findings, the correct clinical diagnosis was made in most cases within 24 hours of admission, when serological tests are still negative, using a combination of criteria (to be published).

During the past 18 months, the incidence of cases in the population of Nottingham has been 1 per 50 000 per year.

ACKNOWLEDGEMENTS

We would like to express our thanks to colleagues in the Pathology Department, City Hospital, the Nottingham Public Health Laboratory (in particular Dr A. D. Macrae and Dr M. J. Lewis) and the Center for Disease Control, Atlanta, USA, who have confirmed these cases. We are grateful to the consultant physicians at this hospital for permission to describe their patients, and particularly Dr D. Davies, Dr W. H. Roderick Smith and Dr R. P. Burden for advice on the manuscript.

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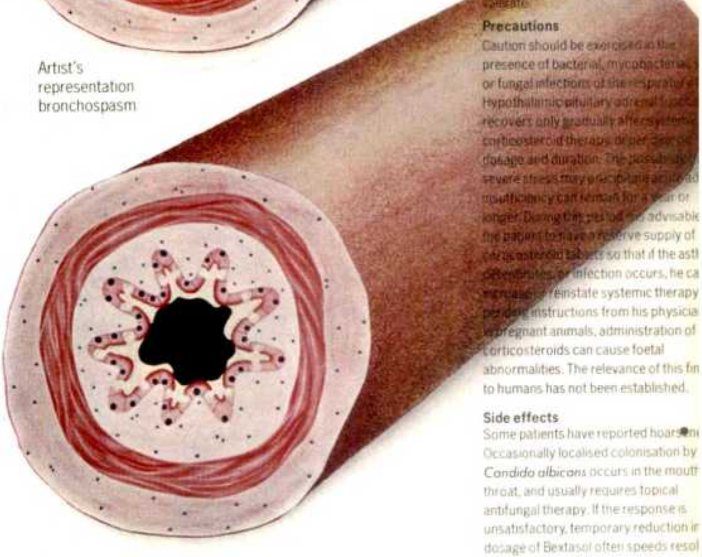

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and children is 800mcg daily, usually a
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asthma is complicated by hypersecret
of mucus, Bextasol may not reach the
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therapy may remedy this. Provided the
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reduced slowly over a few weeks to the
minimum necessary to obtain control.
Where severe asthma has required
maintenance treatment with systemic
corticosteroids or ACTH, these may be
reduced, or even withdrawn eventually,
the equivalent of [illegible] prednisolone per
at weekly to monthly intervals, but grea
care is necessary in case of pituitary or
adrenal hypofunction. Corticosteroid
withdrawal symptoms including anore
nausea, vomiting, muscle and joint pair
may occur. Furthermore, atopic condit
such as rhinitis and eczema, which wer
suppressed by systemic corticosteroi
may be unmasked, and require therapy

Contra-indications

Hypersensitivity to betamethasone
valerate.

Precautions

Caution should be exercised in the
presence of bacterial, mycobacterial
or fungal infections of the respiratory
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recovers only gradually after systemic
corticosteroid therapy, depending on
dosage and duration. The possibility
severe stress may precipitate acute ad
insufficiency can remain for a year or
longer. During this period it is advisable
the patient to have a reserve supply of
corticosteroid tablets so that if the asth
deteriorates, or infection occurs, he ca
increase or reinstate systemic therapy
pending instructions from his physicia
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corticosteroids can cause foetal
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to humans has not been established.

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Br. J. Dis. Chest (1979) 73, 39

TRIAMCINOLONE IN CORTICOSTEROID-RESISTANT ASTHMA

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Summary

In an uncontrolled study 38 patients with chronic asthma were treated for up to 4.5 years (mean 2.9) with depot injections of triamcinolone acetonide. About half had proved difficult to control on large doses of corticosteroid tablets. Three-quarters were helped and the incidence of hospital admission amongst them was reduced. Side effects were tolerable and adrenal function was only moderately depressed. Spirometry showed continuing improvement up to three years after starting triamcinolone.

Whether similar improvement could have been achieved by a different dosage regimen of corticosteroid tablets or whether it might have ocurred spontaneously was not tested. A controlled trial seems warranted.

INTRODUCTION

The number of asthmatics who appear to require at least 10 mg daily of prednisolone or its equivalent in other synthetic corticosteroids is perhaps less than 10% of those taking corticosteroid tablets. A substantial number of patients of this sort, however, attend hospital asthma clinics. The high dose of corticosteroid tablets can be reduced somewhat by the use of corticosteroid aerosols, but in the authors' experience the asthma usually remains difficult to control and moon face, weight gain and other side effects continue to be troublesome.

This paper describes the results of prolonged administration of triamcinolone acetonide in corticosteroid-resistant bronchial asthma.

Patients and Methods

Two groups of patients requiring long-term corticosteroid administration for control of breathlessness due to bronchial asthma were asked to volunteer to receive intramuscular depot injections of triamcinolone at intervals sufficient to control symptoms. Patients with anaemia, hypertension, ischaemic heart disease, chest deformity or any other disease likely to cause breathlessness were excluded. Non-reversible airway narrowing could not be excluded in some patients.

In the first group patients were already receiving about 10 mg of prednisolone per day, and most had cushingoid features. Symptoms of wheeze and breathlessness were often inadequately controlled for fear of exacerbating side effects with higher corticosteroid dosage. In the second group prolonged corticosteroid administration had not been tried but was now considered necessary because of failure to control symptoms.

Before starting triamcinolone injections pulse, blood pressure, body weight, forced expiratory volume (FEV_1), forced vital capacity (FVC), and 9 a.m. basal plasma cortisol were recorded, followed by a short synacthen test (0.25 mg intravenous synacthen) recording plasma cortisol at 30 min, 1 hour and 2 hours after injection.

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* Present address: The East Birmingham Hospital, Birmingham.

Triamcinolone acetonide was administered in a standard dose of 80 mg by intramuscular injection. Administration of oral and aerosol corticosteroids was stopped, but patients continued to take sodium cromoglycate or bronchodilators such as salbutamol, ephedrine or aminophylline derivatives. Visits to the out-patient clinic were made initially at weekly intervals where pulse, blood pressure, body weight and spirometry were recorded. Wheeze and breathlessness improved after the first injection but recurred after an interval. At this point the injection was repeated and a therapeutic interval established for the patient. Thereafter appointments were made at this interval of time. A careful note of side effects was made. Basal 9 a.m. plasma cortisol levels and synacthen tests were repeated at yearly intervals.

Results

Thirty-eight patients agreed to the study, 21 women and 17 men. The mean age at entry was 52 years (SD ± 12). Twenty-eight patients have been followed up for at least 1 year and eight of these for as long as 4 years (mean length of treatment 2.92 ± 1.0 years). Of the rest (ten), seven have had less than 6 months' follow-up to date, two were lost to follow up after 1 year's treatment and one died in respiratory failure after 2 months' therapy. One other patient (included in the main 28) died in respiratory failure after 2½ years on triamcinolone. One patient who had less than 6 months' therapy made such good improvement that therapy was stopped. All the graphical data are based on the main group of 28 patients, though clinical results and side effects include all patients.

Of the main group of 28 patients, 15 had been taking oral prednisolone for a mean period of 8.2 ± 6.6 years in a mean dose of 10.8 ± 4.4 mg daily. The remaining 13 had not been taking corticosteroid tablets regularly, but most had received short courses for particularly severe exacerbations.

Wheeze and breathlessness had been suffered by the patients for 16 ± 12 years before study. All had asthma in the sense of partially reversible airway narrowing as a major component of the illness. The majority fitted into the vague category of intrinsic or late-onset asthma. Four patients had classical extrinsic asthma, nine had associated chronic bronchitis and one had alpha$_1$-antitrypsin deficiency.

About half of the patients (15 of 38) have been maintained on 80 mg of triamcinolone monthly over the whole study period; ten others have needed 80 mg only every 5–6 weeks. One man has needed 80 mg 3-weekly for most of the time. All the other patients are controlled on 40–60 mg every 4–6 weeks, the lowest dose being used is in one woman patient on 40 mg 2-monthly. The mean dose for all patients was 67 mg per month. Assuming that triamcinolone has at most 20% greater glucocorticoid activity than prednisolone (Liddle 1961), this is equivalent to a dosage of 2.86 mg of prednisolone daily.

Symptomatic improvement was assessed on the basis of frequency of attacks requiring the doctor at home or by admission to hospital, time off work, exercise tolerance, (assessed by the MRC grading of dyspnoea) and prescription of inhalers. Table I shows the results: 71% were much better, 29% unchanged. The response was rather better in those who had not received prolonged corticosteroid administration in the past. Hospital admissions with status asthmaticus (defined as breathlessness too severe to walk or talk) were compared for equal periods before and after treatment in each patient. Before triamcinolone administration there were 26 admissions, and after there were 15. If the cases of two patients with intractable asthma are removed the figures become 21

Table I. Symptomatic benefit

	Worse	*No better or transient improvement*	*Good response*
All patients (38)	0% (0)	29% (11)	71% (27)
Continuous previous corticosteroids (20)	0% (0)	35% (7)	65% (13)
Intermittent or no previous corticosteroids (18)	0% (0)	22% (4)	78% (14)

before triamcinolone and four after, suggesting that a substantial number of patients became more stable. They were distributed equally between patients with and without previous prolonged corticosteroid therapy.

Perhaps the most interesting feature is the long-term functional change, and Fig. 1 plots the spirometric findings. After an initial improvement of FEV_1 and FVC a secondary phase of steady increase, particularly of the FEV_1 is observed, and is still continuing in patients treated for 3 years. At 4 years there appears to be a slight fall-off, but only eight patients have been treated for this length of time. The pattern was similar whether or not patients had had continuous previous corticosteroid administration. The FEV_1/FVC ratio increased also, but the slight fall-off at 4 years is again shown.

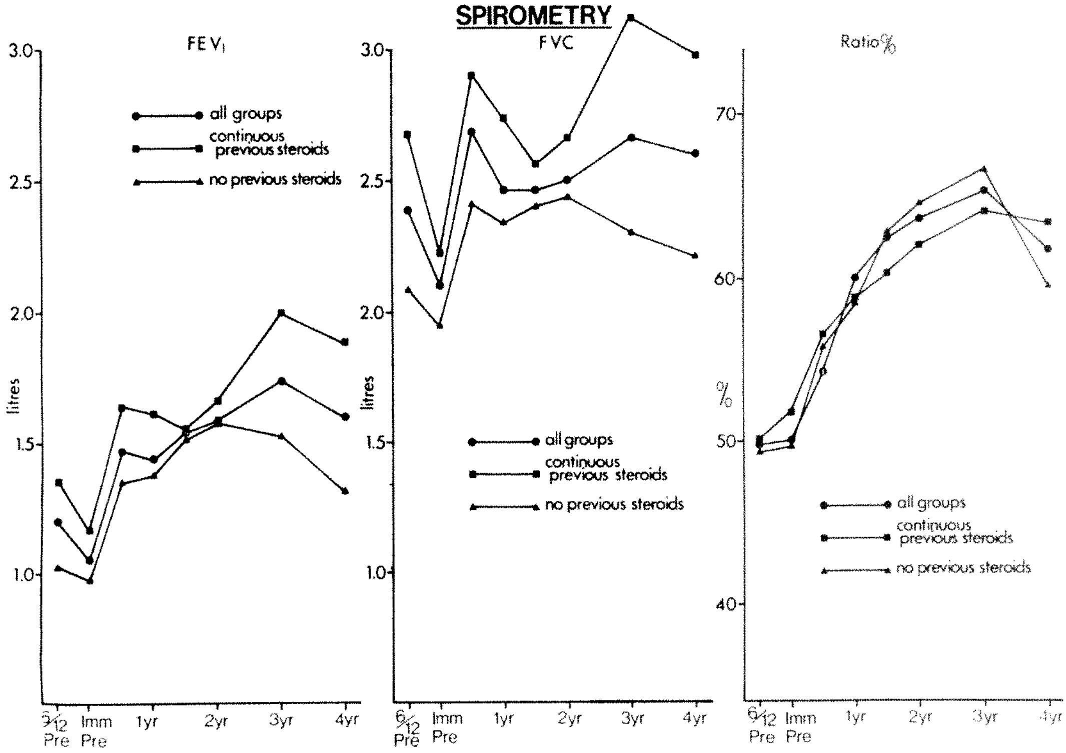

Fig. 1. Functional change

Fig. 2 shows the response to synacthen testing. The expected fall is witnessed in all patients but was not as severe as might have been anticipated. Even after 2 years patients not on continuous corticosteroids previously showed group mean values still within the normal range. Patients on continuous prednisolone had depressed responses but were apparently no worse after two years on triamcinolone.

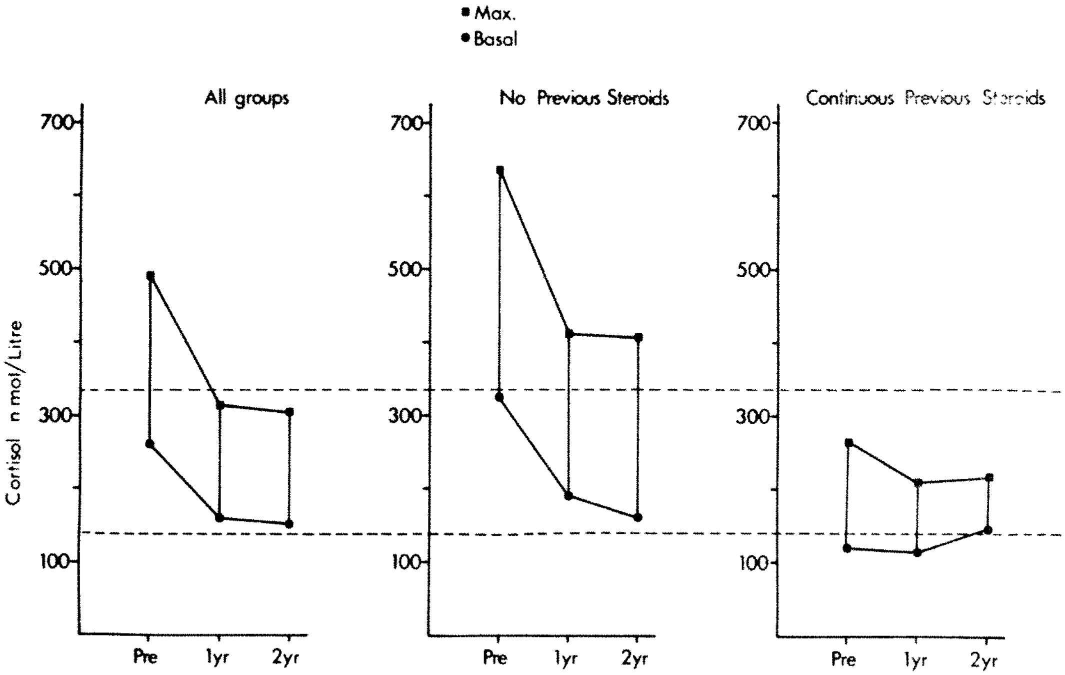

Fig. 2. Respose to synacthen, using 0.25 mg intravenously. Dotted lines indicate the normal lower limits of basal serum cortisol (140 nmol/litre) and of serum cortisol after synacthen (335 nmol/litre)

Table II lists recorded side effects. These were asked for at intervals throughout the study. Moon face and obesity improved. Fig. 3 plots the weight change and shows that the weight gain on previous prednisolone was lost. Purpura was notably worse and there were four cases of mild hypertension. One man developed proximal myopathy and he also developed cataracts. Another man had developed a proximal myopathy on previous therapy with ACTH but has since not deteriorated on triamcinolone. Two cases of gynaecomastia attributed to ACTH improved considerably when therapy was changed.

Discussion

In this pilot study of depot triamcinolone the patients were mainly asthmatics of late onset. Most were a good deal better controlled than previously, particularly those previously taking high doses of prednisolone. It is of interest that a much lower mean corticosteroid dose achieved better symptomatic and functional control. The initial spirometric improvement was followed by futher long-term increase which could be interpreted as evidence for two components to reversibility. The first, short-term, changes were

Table II. Pattern of side effects

Side effects	*Previous steroids*	*Improved on triamcinolone*	*New or worse on triamcinolone*
Cushingoid facies	9	5	1
Cushingoid obesity	11	9	0
Hirsutes	1	0	1
Bruising/purpura	5	1	10
Poor healing/thin skin	0	0	2
Acne	0	0	1
Pigmentation	2	2	0
Gynaecomastia	1	0	0
Oedema	0	0	1
Fat necrosis at injection site	0	0	1
Hot flushes after injection	0	0	1
Mild hypertension (not needing therapy)	1	0	4
Osteoporosis	3	0	1
Diabetes mellitus (oral therapy)	0	0	1
Dyspepsia (barium negative)	2	0	2
Cataract	0	0	1*
Proximal myopathy	1‡	0	1*‡
Clinically significant hypoadrenalism	1	0	0

* Occurred in the same patient. ‡ Different cases.

Figures refer to the numbers of patients with each side-effect. The first two columns only include patients on continuous previous corticosteroids; the third column refers to all 38 patients.

attributable to bronchial muscle relaxation, reduction in bronchial mucosal oedema and reduction in secretions. The second, a long-term phase, may be related to anatomical changes in the airway—perhaps a reversal of some of the smooth muscle hypertrophy so often demonstrated pathologically (Gough 1960; Dunnill et al. 1969).

The functional response to triamcinolone was virtually identical in both the group who had previously received continuous corticosteroids and the group who had not. It seems therefore that the patients on regular corticosteroids had been functioning well below their potential, despite developing systemic side effects.

The pattern of side effects was not clearly worse or better. Patients were particularly gratified by the weight loss, which was almost certainly due to loss of fat. Only one case of muscle disorder was seen. The much feared myopathy of triamcinolone has not been a problem, presumably because of the low doses employed. Suppression of adrenal function was no worse than with prednisolone therapy. There is every reason to believe that, in the longer term, control with the low doses of triamcinolone employed would lead to less side effects than would be expected from 10–30 mg of prednisolone daily. It is in the relatively prednisolone-resistant patient that the depot steroids might have their greatest value. Non-steroid-dependent asthmatics being treated for the first time

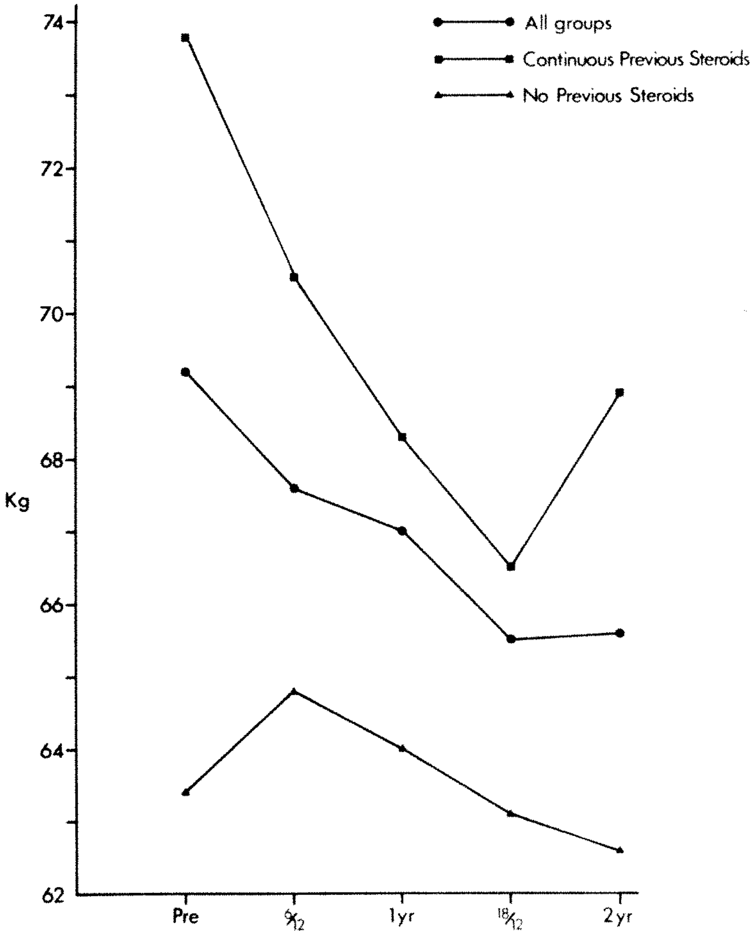

Fig. 3. Weight change.

can be readily and conveniently controlled with triamcinolone depot but it seems probable that side effects would be unacceptable compared to low doses of oral prednisolone.

Thus in an uncontrolled study, a lower dose of corticosteroid in the form of a depot preparation of triamcinolone acetonide was more helpful in relieving symptoms in corticosteroid resistant late onset asthma than a higher dose of prednisolone tablets. The improvements, where they were observed, were maintained and confirmed spirometrically. A controlled trial seems warranted.

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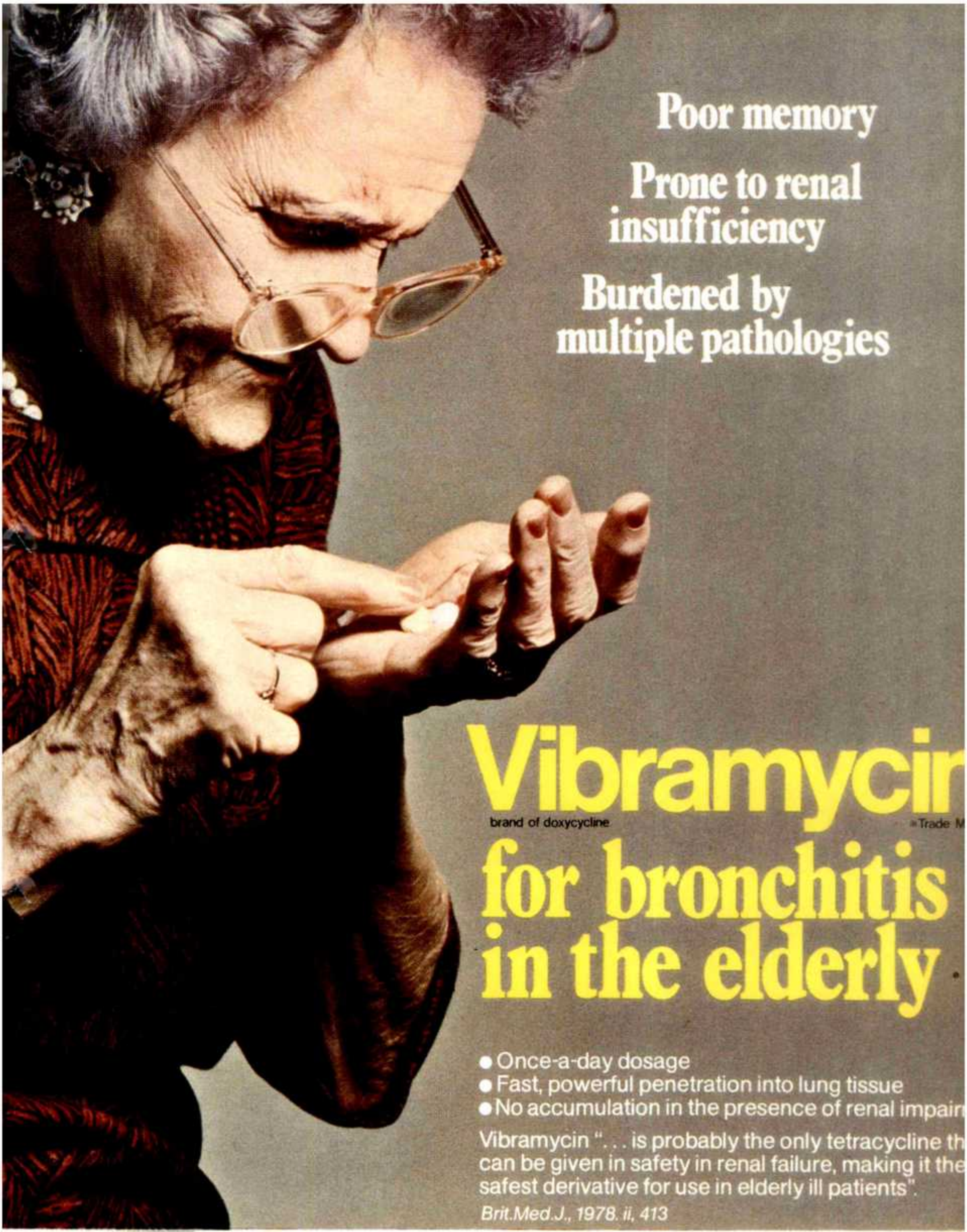

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Brit.Med.J., 1978. ii, 413

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References: 1 Lancet 1976, **2,** 616. 2 Data on file Squibb Institute for Medical Research.
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Br. J. Dis. Chest (1979) *73*, 45

PROGRESS IN THE PREVENTION OF CHEST DISEASE: A ONE-DAY CONFERENCE IN MEMORY OF HORACE JOULES

edited by
MARTIN W. MCNICOL

Horace Joules born 21 March 1902, died 25 January 1977. MD(Lond.) (Gold Medal), FRCP, Senior Physician, Central Middlesex Hospital 1935–64 and Medical Director 1939–64. Former member of the North-West Metropolitan Regional Hospital Board and the Central Health Services Council.

A one-day conference in memory of Horace Joules was held in the Avery Jones Post-graduate Centre of the Central Middlesex Hospital, London, on 27 January 1978. In addition to the papers presented here, the following were also read:

Professor D. L. Miller discussed the importance of influenza and considered it to be the most disruptive and distressing of all acute respiratory infections, and despite certain recent advances it remained a great challenge to preventive medicine.

Mr Laurie Pavitt MP considered parliamentary response to prevention, noting that the Government had only accepted 24 of the 58 recommendations of the recent report of the Select Committee on Preventive Medicine. He considered that the fundamental problem for action on prevention was education and that it was needed not least in the Palace of Westminster.

Dr J. H. Edwards presented a paper on Organic Dusts and Disease in which he reviewed the various factors governing the pulmonary response to these agents.

SESSION I. *Chairman:* Sir Francis Avery Jones

Horace Joules and the Central

KEITH BALL

Horace Joules's passion for the prevention of chest disease was based on daily experience in his own patients: young women with tuberculosis, older men with chronic bronchitis or lung cancer, and miners crippled with chest disease. He became angry when he saw his patients suffering needlessly from their environment or from their own habits.

Tuberculosis at the end of the war was a serious problem and by 1949 there were 11 000 patients awaiting admission to sanatoria. The high incidence amongst nurses was causing anxiety and many general hospitals refused to admit tuberculous patients. In 1945 two wards for tuberculosis were opened at the Central Middlesex Hospital. To protect the nurses Horace insisted that only the Mantoux-positive should work there. In addition they wore gowns and masks for bed making. Every effort was made to discover undiagnosed cases in the hospital and they were immediately transferred to these wards. As a result hardly any nurse developed the disease, and their Mantoux conversion rate was much lower than nurses working in either the old LCC hospitals or the London teaching hospitals.

Horace felt deeply about his patients with chronic bronchitis. The disease was much more frequent then than today. The black smog of December 1952 galvanized him into action. In a letter to the *Lancet* that year (1953*a*), Horace wrote, 'I live 300 yards up wind from a large power station. As dawn breaks one can watch a billowing cloud of cooling steam float from the cooling towers. This often extends across the sky for two or three miles; into it the power station chimney belches huge quantities of unwashed smoke and grit. Under favourable weather conditions this goes on for hours; the sun is blotted out and a drab half-light replaces its rays. On other days we are not so fortunate for the water vapour descends on the main road and brings traffic almost to a standstill.' To the *British Medical Journal* (1953*b*) he wrote 'I believe we shall not progress in the prevention of this and other chest diseases until we regard a persistent cough as seriously as persistent vomiting . . . The air we breathe is as important as the water we drink. It must be uninfected and unpolluted. A sanitary revolution commencing a hundred years ago has done much to eliminate water-borne disease. We should work to the elimination of bronchitis and other air-borne disease.'

After a visit to Sheffield he wrote again to the *Lancet* (1953*c*), 'Not long ago I sat in a churchyard not far from a maternity hospital in that city. In the countryside it was a beautiful spring morning, but in Sheffield the sun showed through a haze of smoke and dirt. I held out a hand and smuts almost a centimetre in diameter fell on it. I wondered how many children being born in the hospital would die, victims of the atmosphere.' He would have been happy to have seen how much cleaner Sheffield is today.

Horace was particularly concerned about chest disease in miners. To the *Lancet* (1953*d*) he wrote, 'In London I see a number of miners with dust disease. Thousands left the pits during the great depression; many walked to London seeking work. One such came to my out patient clinic a few weeks ago with early congestive failure. When asked if he had visited his native valley lately he replied, "Yes I have been home three times in the last 6 months to bury the only remaining miner friends I have. They each died of what I have got".'

Following Doll and Hill's work in 1952 he campaigned strongly against cigarette smoking. As a member of the Standing Medical Advisory Committee he helped to persuade the Medical Research Council to make the first public pronouncement on the association between smoking and lung cancer. He had been a very heavy cigarette smoker for 30 years but had managed to break his own addiction. In the *Lancet* (1956) he wrote, 'Cancer of the lung continues to cause more and more deaths. It is in the approach to this grave national problem that the Ministry of Health has manifested its weakest aspect. The upward trend of mortality shows no signs of abating . . . Unless this is modified, a million people in England and Wales will die of this cancer before the end of the century. It is as though a city the size of Leicester were to be wiped out leaving no person alive. So far the Minister of Health has refused to accept the advice of the Standing Medical Advisory Committee which has counselled continuous education of the public about the risks of cigarette smoking.' His prediction was more than justified. The one million deaths he forecast will be reached by 1987 if the annual deaths from lung cancer remain at more than 30 000 a year. He continued; 'An opportunity to take part in preventive activity now presents itself to each one of us by personal abstinence, thus strengthening the advice we give in relation to the harm resulting from this addiction. The Royal College of Physicians can re-enact history and help to revivify itself by giving advice comparable to that given in respect of alcohol 200 years ago.' Fortunately the College did take this advice and six years later published its historic report on *Smoking and Health*.

In 1955 he commented; 'The evidence of many countries confirms the findings of Bradford Hill and Doll that tobacco consumption especially in the form of cigarettes is the main factor in the aetiology of this cancer. The Ministry of Health attempts to shroud this fact in mystery. The Chancellor of the Exchequer asks that the population continues to smoke, and meanwhile there is joy in the City over increased dividends from the sale of this carcinogen. . . . No narcotic has ever caused such wide-spread havoc as tobacco now does throughout the Western world. The later days of the patient dying from cancer of the lung are tragic; the later years of the chronic bronchitic clutching his cigarette are pathetic. By our example and by precept we could raise preventive medicine to the place it must occupy if much lung disease is to be eradicated.'

It is sad that 20 years later governments and health ministers are still so timid in their approach to the control of cigarette smoking, our main environmental cause of death. They still seem satisfied that voluntary agreements will suffice to curb an industry which causes nigh on 70 000 deaths a year.

One can now assess Horace Joules's main contributions to medicine. He was an outstanding physician much loved by his patients and greatly respected by his colleagues. He was a great medical administrator who helped unite all the hospial staff in a common objective. He was an outstanding teacher who left his mark on many students and doctors practising in various parts of the world. He will, I believe, best be remembered for his contribution to preventive medicine. He showed that the individual doctor can help to effect change in medical and social policy. He sowed the seeds of prevention in the minds of many practicing doctors. He made a major contribution to the prevention of tuberculosis, bronchitis and lung cancer over the last 30 years.

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Lung Cancer: Prospects for Control

RICHARD DOLL

That smoking, and particularly the smoking of cigarettes, is a cause of many cases of lung cancer is now so widely accepted that there is no need to review the mass of evidence that supports it. In theory it is just possible to explain the many observed associations in other ways. It could occur if there was a gross bias in favour of diagnosing lung cancer in cigarette smokers; or if there was a genetic factor that determined both selection into a high risk groups and susceptibility to the disease. This last concept is capable of being tested by studying pairs of twins whose smoking habits differ. The data from the Swedish Twin Register are, as yet, too few to settle the matter, but so far as they go, they point to a direct effect of cigarette smoking and a minimal effect from genetic differences.

The basis for a programme for prevention rests on four observations:

1. The rarity of lung cancer in non-smokers in practically all circumstances, including exposure to atmospheric pollution with coal smoke and to some occupational dusts. The only clear evidence for a moderately high risk in the absence of smoking relates to adenocarcinoma of the bronchus in Chinese women in Singapore and Hong Kong.

2. The absence of a threshold limit to the amount of smoking below which no effect is produced. It is, however, uncertain whether the risk increases in proportion to the dose of smoke or to the square of the dose.

3. The benefit from stopping smoking is evident within five years.

4. The risk for an ex-smoker at any given time after stopping is determined by the length of time he had smoked before he stopped.

Discouragement of smoking has been the official policy of the Department of Health and Social Security since 1957, but the response by the public has not as yet been very great. Three important changes have, however, occurred. First, men in the Registrar General's top social class (constituting 4% of the population) have more than halved the number of cigarettes smoked per day since 1958 (from 10.9 to 5.1) while male doctors have reduced by even more. Secondly, there has been a gross change from the smoking of plain cigarettes to filter-tipped cigarettes which constituted 2% of the market in 1955 and 87% in 1975. Thirdly, the industry has modified the type of cigarettes sold, so that the amount of tar delivered by the average cigarette when smoked in a standard way has been reduced by 43% since 1965. How much tar was delivered before then is unknown but is now being investigated. In contrast, it has to be recorded that cigarette sales per adult *increased* between 1950 and 1973 (from 6.0 to 8.8 a day) before falling slightly in the next two years. The major part of the increase was due to increased smoking by women, but there was also some increase by men possibly due to the decreased content of nicotine.

At the same time as these changes there has been a reduction in the mortality from lung cancer among men of up to 75 years of age and a material reduction under 45 years of age, so that the total number of deaths fell in 1975 for the first time for 50 years. In women the mortality has increased at all ages over 45 years; at younger ages there has been a small decrease, but much smaller than in men.

For the future, three approaches to prevention are possible:

1. The manufacture of less noxious cigarettes.
2. Government intervention to restrict sales.
3. Health education.

The first has many attractions and has almost certainly made a major contribution to the reduced death rate from lung cancer in men in the last 10 years. The objection to it is that we do not yet know which components of cigarette smoke are responsible for the many different diseases that can be caused by smoking. Chronic bronchitis is diminishing rapidly, due probably in part to improvements in social conditions during childhood and to reduction in atmospheric pollution, and this reduction has accelerated since low tar cigarettes began to be introduced. The same is not true, however, of ischaemic heart disease which has shown no signs of a reduced incidence in any age group. This may be because changes in diet have operated to increase the incidence of the disease or because the noxious factor in cigarette smoke is independent of the tar content, as is, for example, carbon monoxide. The manufacture of 'less noxious cigarettes' will, therefore, remain a risky method of prevention until we known what components of smoke are noxious.

Government action is crucial.

Finally health education may well be much more effective in the future than it has been in the past. It is not only doctors and health workers who have given up smoking but also many teachers, writers, journalists, actors, producers and university students. Health educationalists now have, for the most part, the active support of the media and in these circumstances knowledge is as infectious as measles. Education has not failed: it has rather established a position from which it can expect to advance with every prospect of success.

The Prevention of Chronic Bronchitis

C. M. FLETCHER

In a letter to the *British Medical Journal* in 1953 Horace Joules said that the main causes of damage to the lungs in chronic bronchitis were 'the irritant effect of cigarettes combined with general atmospheric pollution of our industrial cities and the vitiated atmosphere of factory, foundry and mine, producing a chronic and deteriorating condition which is made worse by each winter's virus infections.' He thought that years of coughing and infection ultimately led to the disabling breathlessness which he described as a sort of asthma. Since Horace's day our ideas about the causes of bronchitis and its natural history have changed in many ways.

Cigarettes have been shown in many surveys (US Public Health Service 1971) to be a major cause of chronic cough and expectoration, though many smokers remain free from these symptoms. Most of those who have a cough lose it when they stop smoking. Chest infections are more common in smokers, especially those who cough. Surveys have also shown that average lung function is reduced in smokers, but few of them have reported how many smokers retain normal function. Clinical series and autopsies have shown that severe disablement or emphysema is rare in non-smokers (Fletcher 1977*a*, *b*). Only one non-smoking doctor died of bronchitis in the 20 years of the study by Doll and Peto (1976). In all these studies the low risks of ex-smokers has shown the protective value of stopping smoking.

Air pollution has, undoubtedly, been important, but is now much less important than the cigarette.

Industrial dust. With his concern with South Wales, Horace insisted that the dust in the mines caused bronchitis as well as pneumonconiosis. He did not realize how much more harmful were the cigarettes that the miners smoked. Dust has never produced much bronchitis itself (Gilson 1970), and with modern dust control can now be almost discounted.

Social class. It is odd that in spite of his concern with injustices of the under-privileged, Horace did not emphasize poverty and social deprivation as a cause of chronic bronchitis, although it is powerfully associated with seriously disabling and fatal bronchitis. The ratio of bronchitis mortality in unskilled labourers to that in professional classes was about 5:1 in 1931 and was much the same in 1971 despite a marked decline in bronchitis mortality in all classes. No one has yet advanced a convincing hypothesis about what aspect of social deprivation damages the lung.

Bronchial infection. Horace's opinion that infection plays a major role in damaging the lung has persisted without any supporting clinical or epidemiological evidence (Fletcher 1976). Our own studies of factors affecting the rate of development of airflow obstruction (Fletcher et al. 1976) showed that if clinical infections had any effect at all it was too small to be detected.

Prevention of bronchitis. We have not done too badly in spite of the increase of cigarette smoking which caused the great increase of lung cancer in the last half century. Bronchitis mortality over the same period remained constant at first in men while declining in women. It is now declining faster in men than in women. This means that some causative agent must have been reduced in severity to cancel out any increase due to the cigarette. This agent cannot have been air pollution, for the air of our cities was not cleaned until about 1960, nor can it have been infection for the decline in women started before antibiotics were available. Perhaps the decline has been due to improved standards of living reducing the unknown effects of poverty in all social classes!

The importance of cigarette smoking as a cause of bronchitis has been re-emphasized in our prospective study (Fletcher et al. 1976). It was the only factor that we found to be causally related to the rate of deterioration of lung function, and our non-smokers all had normal function. If all cigarette smokers were to stop smoking, chronic airflow obstruction with its attendent disablement and mortality would disappear within a generation. Despite all our efforts to persuade smokers to stop, the numbers who have done so are not large, but the big reduction in the percentage of smokers among doctors and other men in social class 1 does provide us with grounds for hope (Royal College of Physicians 1977).

Our study (Fletcher & Peto 1977) suggested an alternative line of attack. Only a minority, perhaps less than 10% of moderate and 20% of heavy smokers, develop disabling airflow obstruction. Smokers who are going to be seriously affected can be detected by simple methods of spirometery such as forced expiratory volume in 1 sec, or the Wright peak flow meter, long before they are disabled. Because of the wide range of normal values, however, these tests may show up a number of doubtful, borderline cases. There is now evidence that those with normally low values (who have a good prognosis) could be distinguished from those with similar values due to a decline from a previously higher level in early life which will continue to deteriorate. This could be done by tests such as the expiratory nitrogen slope or the maximum flow rate at 25% of vital capacity ($\dot{V}_{max25}$) (Fletcher 1977*a*, *b*; Tattersall et al. 1978). Such smokers could be vigorously persuaded to stop or to adopt less hazardous forms of smoking. This might not prevent severe disease entirely, but it might greatly reduce its prevalence and deadly effects and thus prevent much of the misery that it still causes.

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Asbestosis and Mesothelioma

PETER ELMES

While collecting patients for an MRC trial of antibiotic therapy in bronchitis in Belfast in 1959 Professor Owen Wade and I recognized cases of lower zone fibrosis in shipyard workers, some of whom also had pleural plaques. At the same time two cases of diffuse pleural malignancy came under our care and were diagnosed as mesothelioma by Dr Elliott McCaughey who had already described 15 cases of this supposedly rare tumour in Belfast. On a visit from South Africa to discuss these tumours Dr Wagner suggested that they might be due to asbestos exposure. As the lower zone pleural disease cases had also suggested asbestos exposure, Professor Wade and I embarked on a study, the results of which have been summarized recently (Elmes 1977).

There were two occupational groups directly exposed to asbestos in the city: the insulation workers or laggers employed by contractors to work both in the ships and in the factories and power stations, and a small group of women filling asbestos cloth insulation quilts with asbestos fibre in a back-street factory. There were between 150 and 250 insulators at any one time and although they moved from contractor to contractor they proved to be a stable population with close social and family ties, but the men died young and the widows married again, often within the same group, some losing two husbands with cancer before reaching retiring age themselves. Investigation of the men still at work revealed only an increase in the incidence of radiographic abnormality and minor disability compared with other men of the same age. Mortality studies, however, revealed the full extent of the hazard which had been recognized by the workers but not by the medical profession or the health authorities.

It was possible to trace the fate of 162 of the 168 men who were working as insulators in 1940. Their excess mortality was mainly due to respiratory cancers, about two-thirds of which were primary bronchial carcinoma and one-third mesothelioma. There was a small excess of cancer of the gastrointestinal tract and of death due to respiratory failure in the earlier years. Of those who were traced 98 had died and age-adjusted predictions predicted the death of only 37. It is extraordinary that such a level of hazard could have remained unrecognized. Such evidence as has been collected indicates that the hazard for all insulation workers in Britain was the same. Conditions have changed in the last 10 years and these men seldom apply new asbestos insulation. Many now refuse to strip old asbestos insulation and this is left to specially trained groups employed by demolition contractors and is work which carries the highest risk remaining in the asbestos industry.

Our studies indicated that asbestosis and mesothelioma (of occupational origin) in Belfast was all arising as a result of the insulation work. Studies of the lungs of unselected cases of lung cancer indicated that asbestos was not a significant contributory cause except in men exposed to insulation material. It will take many years to determine whether the replacement of asbestos by other materials for insulation purposes has been effective. Present evidence suggests that the substitutes (various type of man-made fibres) are unlikely to cause lung fibrosis or act as an adjuvant to cigarette smoking in causing lung cancer. But animal studies have raised the possibility that mesotheliomas may be caused by many mineral fibres provided the size and shape was right. Preliminary observation in Anatolia in two villages where there is a very high incidence of mesothelioma suggests that other fibres may be involved. There is no significant exposure to asbestos and the environment in these villages is in every way identical to that of neighbouring unaffected villages, save that the soil in the area is derived from the soft volcanic tufa which is also used for building houses, for stores for food and material. There is reason to believe that the high incidence of mesothelioma is due to the presence of a fibrous silicate other than asbestos which is present in the tufa in some villages but not in others.

If the production of mesotheliomas in humans is due to exposure to mineral fibres of a certain size range irrespective of the chemical composition, then the current practice of replacing asbestos by man-made fibres may be ineffective in preventing disease unless accompanied by stricter dust suppression.

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SESSION II. *Chairman:* Sir George Godber

Tuberculosis in Brent

MARTIN W. MCNICOL

In the late 1950s there were approximately 300 new cases a year of tuberculosis in Willesden with a high mortality. In a vigorous pioneering approach to the problem, Hugh Toussaint, with considerable assistance from Horace Joules, instituted an outstanding scheme of domiciliary treatment. Patients treated at home showed a recovery rate as good as was then available with sanatorium treatment. The incidence of tuberculosis fell considerably after the introduction of chemotherapy and by the mid-1960s was approximately 200 per year. Since then the incidence has risen once more so that in 1975 there were again 300 cases a year. The rise in incidence has affected almost exclusively the immigrant community, initially the Caribbean immigrants and subsequently East African and Asian immigrants. The peak incidence in 1975 followed three years after the peak immigration in 1972. The majority of immigrants on arrival have a positive tuberculin test. The disease incidence in immigrants has been greatest within five years of arrival. Very few have had obvious active disease at the time of arrival and the development of the illness appears to be related to the breakdown of pre-existing stabilized infections.

Along with the increase in incidence there has been a diversification in the types of disease seen. Extrapulmonary disease now accounts for 40% of the total cases. Lymph node disease affecting the cervical nodes is the most common. Joint and bone tuberculosis has reappeared; approximately 30 new cases are seen each year. The pattern of bone disease has changed, particularly that of spinal tuberculosis, where disease of the posterior elements is more common.

Microbiological studies of material from all forms of disease have shown organisms which are exclusively human-type organisms, predominantly of East African strains and possibly of slightly reduced virulence. Drug resistance has been uncommon. Treatment policies have been changed to minimize hospital admission. Domiciliary chemotherapy is given using basically rifampicin and isoniazid. Where possible hospital and surgical treatment has been avoided. The results of this approach appear to be excellent. The increasing incidence of tuberculosis has been dealt with at a substantial reduction in hospital bed usage and the incidence of tuberculosis is beginning to fall again.

Since December 1976, in an attempt to prevent development of active disease immigrants without clinical or radiological evidence of tuberculosis but with a strongly positive tuberculin test have been given prophylactic chemotherapy with isoniazid and ethambutol. This scheme has now been extended by the establishment of an Immigrant Clinic at which all new immigrants will be screened and chemotherapy given to strongly positive tuberculin reactors.

BCG policy has also been changed and children are given BCG at birth and in schools the age of BCG vaccination has been progressively reduced. Although there has been a considerable rise in notification, the tuberculin positivity of 5- and 13-year-olds in schools has shown a progressive decline.

In 1977 the number of cases fell to 265. Whether this reduction was a result of the measures taken or whether it reflects the substantial fall in the number of immigrants is not certain. It is possible that the reduction in numbers of immigrants from a peak of 4500 in 1972 to 2000 in 1976 is the more important factor.

Air Pollution

PATRICK LAWTHER

Horace Joules, like many other great men in the field, condemned the evils of air pollution long before the 1952 'smog' and when the MRC was still wondering whether it ought to form a committee to study the effect of pollution on health. He got most of the story right but his hate of Willesden Power Station was only partly justified. He would produce figures to show how pollution was related to distance from the power station. They were good, true figures but they were estimates of 'deposited matter'—coarse grit and dust—which could not get into the lung, though it could and did soil the environment. He spoiled his case whenever he showed a slide of the cooling towers looking dramatic with their plumes of water cloud showing black against the setting sun. In fact almost all the pollution which was so obviously harmful to the health of his patients was from the chimneys of the little houses of the district. This was the only bit of the story he got wrong and how he would rejoice to see the effects of abolishing this source of pollution.

An effort is needed to recall conditions in the 1950s; we were trying to devise 'smog masks to protect patients and public against episodes of what now seem astronomically high levels of coal smoke and sulphur dioxide. There was no difficulty about demonstrating by simple epidemiological techniques the effects of pollution on mortality and morbidity. These techniques have been applied regularly over the last 25 years and effects of present day pollution are not discernible amid the 'background noise' caused by infection, weather and other stresses. All our work on the aetiology of chronic bronchitis today confirms the fact that the habit of smoking is taking over the role of the old-style pollution. In those far-off days there was still reaction to the idea that the factor of overwhelming magnitude in the causation of lung cancer was the smoking of tobacco; we did much work on the chemistry and distribution of carcinogenic polycyclic aromatic hydrocarbons derived from coal smoke in an attempt to assess the magnitude of the 'urban factor'. The diesel engine was suspect (on very inadequate premises) of being the cause of lung cancer and we did work on that with comforting results. But now the scare is back with us, started, no doubt, by those who are too idle to read 'the literature'. Motor vehicle exhausts have continued to keep us busy; there has been agitation about carbon monoxide and though we are sad that this gas is emitted by petrol engines we have failed to find more than about 3% saturation with COHb as a result of exposure to street air whereas we often find 10% COHb in the blood of smokers. Then there was the damaging suggestion that lead from cars was making a dangerous contribution to our body burden. Quite careful work has shown this not to be true. But we are not complacent about any pollutant and there is work for us yet on sulphates, ozone, oxides of nitrogen and many other newer pollutants.

Horace would have rejoiced to have seen the glittering fulfilment of this fight for clean air. He would have been less pleased about the pathetic 'official' action against smoking. But he would have been comforted to know that those who denounced the evil habit are no longer thought of as cranks. He was often called a crank when so many of us knew him to be a prophet. The environment and countless sick people owe much to Horace Joules.

Horace Joules and the Hope of Prevention

GEORGE GODBER

My contacts with Horace Joules were mostly related to the early years of the National Health Service but they began very much earlier. We first met in a Public Assistance Institution of the Kesteven County Council in Lincolnshire when the maternity department of the Central Middlesex Hospital had to find a temporary home during the bombing of London early in the war. That was the best I could offer and he wasn't polite about it. I still think he was wrong then, because he asked far too much, but when I met him as an original member of the Central Health Services Council and Standing Medical Advisory Committee he was still asking far more than he could hope to get and I thought he was right.

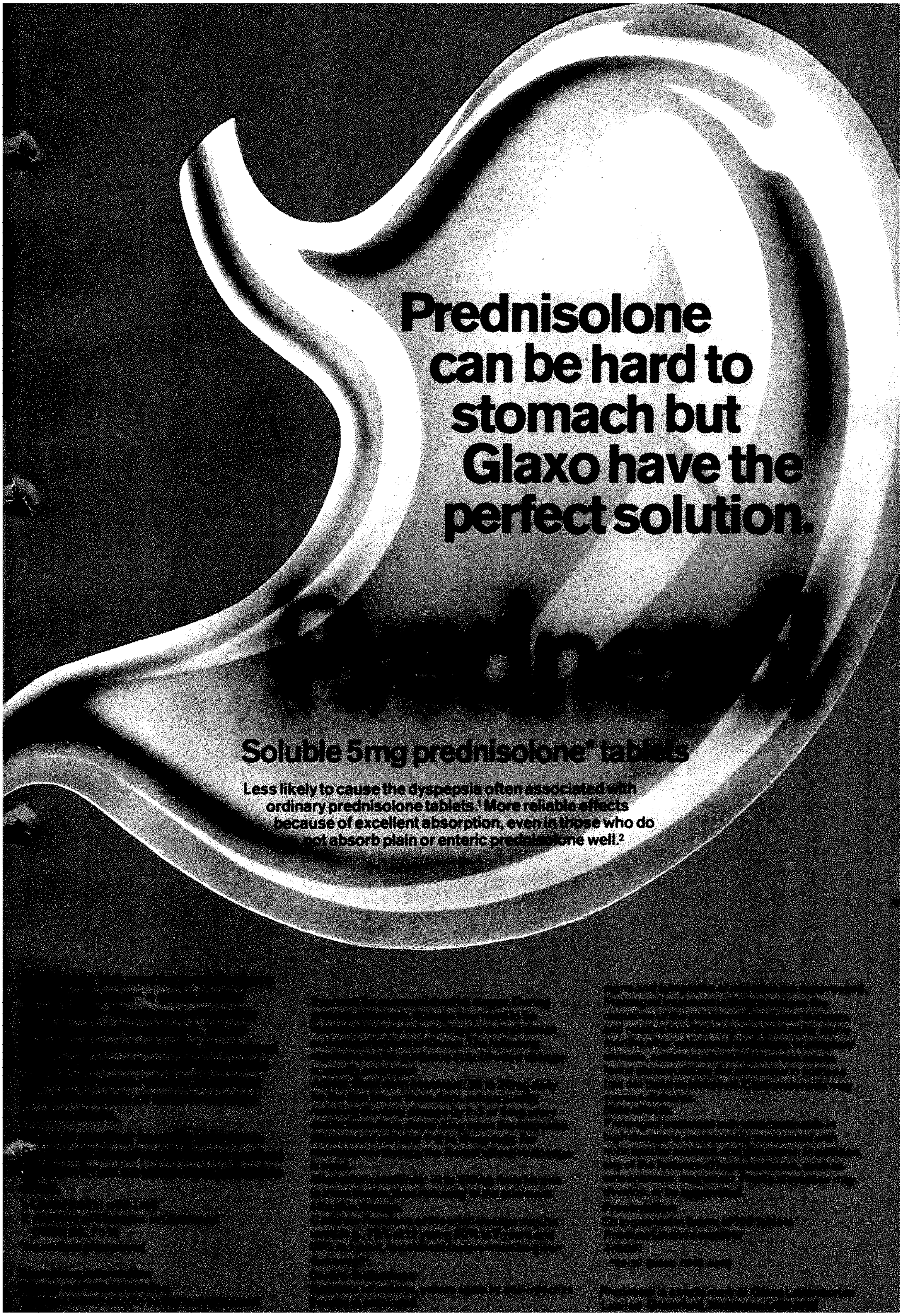
The Standing Medical Advisory Committee was a valuable outside source of expertise and stimulation to the Health Ministry, preventing its autocratic detachment from real life of those working in a district or its general hospital. Through the Committee Horace Joules took a major part in the prevention of chest disease, thrusting to its attention the striking facts about the relationship of smoking and lung cancer as unearthed by Doll and Hill. He also used the Standing Advisory Committee on Cancer to bring further pressure to bear and although the Minister of the day took no urgent action he did ask the Medical Research Council to comment and they finally pronounced that the association of smoking and lung cancer was probably causal. Following on this work came the establishment of the Royal College of Physicians Committee on Smoking and Health. It was their report in 1962 which finally caught public attention and has led to action, which although still inadequate has been taken up by the WHO and now there is a worldwide drive which is beginning to have effect.

Horace Joules also pursued with the Council the problems of chronic bronchitis and pressed for the examination of the relationship between urban atmospheric pollution and mortality from chronic bronchitis before the London smog of 1952 which was to lead to the Clean Air Act. Pressure from Joules helped to find material for the Beaver Committee from which the Act resulted and was possibly also a factor in the MRC's decision to set up Dr Lawther's Air Pollution Unit. Horace Joules was also a constant supporter of any promising development in preventive medicine and it was in the Central Middlesex that the practice of routine miniature radiography of the chest for all newly admitted patients was instituted, that Jerry Morris's Epidemiology Research Unit was established and Tom Garland's Occupational Health Unit set up. Horace's support also enabled Hugh Toussaint to work on tuberculosis within a general hospital and so advance a change in attitude to that disease.

Re-reading some of the earliest reports I have begun to appreciate the philosophical change which has occurred in preventive medicine. The initial measures were primitive, like quarantine; they were then followed by intervention over harmful factors in the environment, pollution of water and food and toxic substances encountered at work. The next stage was health supervision in pregnancy, infancy and childhood. Now we are reaching out to persuade people to change their life-style. Smoking is still currently the largest factor causing premature death and excess invalidity in our society. If we can succeed in reversing the ill effects of this indulgence which has become so widespread there is hope of success against other smaller menaces. The approach to prevention must be pursued through all branches of our comprehensive health service. Where 25 years ago we thought of prevention through environmental change, occupational or general, through specific technical intervention such as immunization and antibiotic prophylaxis or through early diagnosis in mass miniature radiography and screening procedures, a change in approach is now required. Although the Health Service gives a very comprehensive service with great equality of access, there is still far too much waiting for treatment. Preventive measures can reduce the need for care by preventing or postponing the onset of disease. Not only would suffering be greatly diminished but also resources would be released for other forms of care. No country has, or ever will have, the resources of money or trained people to provide everything for everyone without waiting. There must be choices and deliberate deployment of what we have. The health services are part of a broader pattern of social service in which education, sheltered housing, social welfare services and social security cash supports share in a budget which the country may not be able to increase. The development of this major specialist centre at the Central Middlesex Hospital was Horace Joules's life work, but it did not blind him to the claims of other services and he never failed to state them.

Studies such as the UCLA Public Health Study in Alameda County showed that considerable benefits were obtained by those with a life-style characterized by non-smoking, moderated alcohol use, physical exercise, sufficient sleep, a regular pattern of eating and a reasonable height/weight ratio and that large gains are still to be had from adopting such a life style, although the latent period before they are manifest will be considerable. Types of adjustment required in the study were also very different from anything attempted by preventive medicine previously. Prohibitions or specific technical interventions are now unacceptable or unavailable. Patterns of personal behaviour are affected by many extraneous influences and those are often cleverly manipulated for commercial gain. It seems clear that the Government will have to use restricitive powers on the promoters rather than the users, as has been done effectively on promotional expenditure for tobacco products in Norway. Maybe a clearer parliamentary majority will be needed before a Government can be expected to give even a fair wind to such a change here, but it should happen soon. Smoking must remain the largest removable hazard. There are others such as controls on alcohol, the fluoridation of water, and compulsory use of seat belts in cars, or spot checks of blood alcohol by breath analysis in car drivers. Parliament must show that it backs health promotion by legislative action where this is practicable and acceptable. Exhortation is not enough.

The tendency of critics of the health service and some legislators to look for prevention as an alternative for providing cure and care is largely wrong. The balance between social support and health expenditure must be achieved by rational means in which Horace's trenchant realism would have been of tremendous help. The most expensive component of health expenditure is long-term inpatient care. A quarter of all admissions and long-term inpatients are over 65 years of age but five-sixths of them are for short-term care in acute units, over half requiring surgery. This load will be little affected by preventive measures and even if prevention succeeds in raising the age at which coronary artery disease and other atherosclerosis occur, it will still occur but a few years later. The hope of prevention of disease such as cancer certainly seems nearer than that of a generally effective therapy, but even the prospect of greatly accelerating the recent slight reduction of the lung cancer mortality rate takes many years to have a major impact. In the meantime we cannot desist from costly endeavour at treatment. The Health Education Council is now pressing a sustained low-key 'better health campaign'. It tries to put across a message about ordinary living bringing in the key factors like tobacco and alcohol in an incidental way. Whether it succeeds only time will show but I hope it breaks away from health education material in which I have always thought we were talking to ourselves. Even though doctors have three times the standard mortality rate for certain alcohol-related diseases I do not think we should be our own main targets. I am sure that Horace Joules would have seen the fallacy of the prevention versus cure argument that is now too common: we need both. He was the activator of progress on chronic bronchitis and lung cancer and he would have seen the importance of our great need to help educate the less well off in matters of health and help improve their environment at work and at home.



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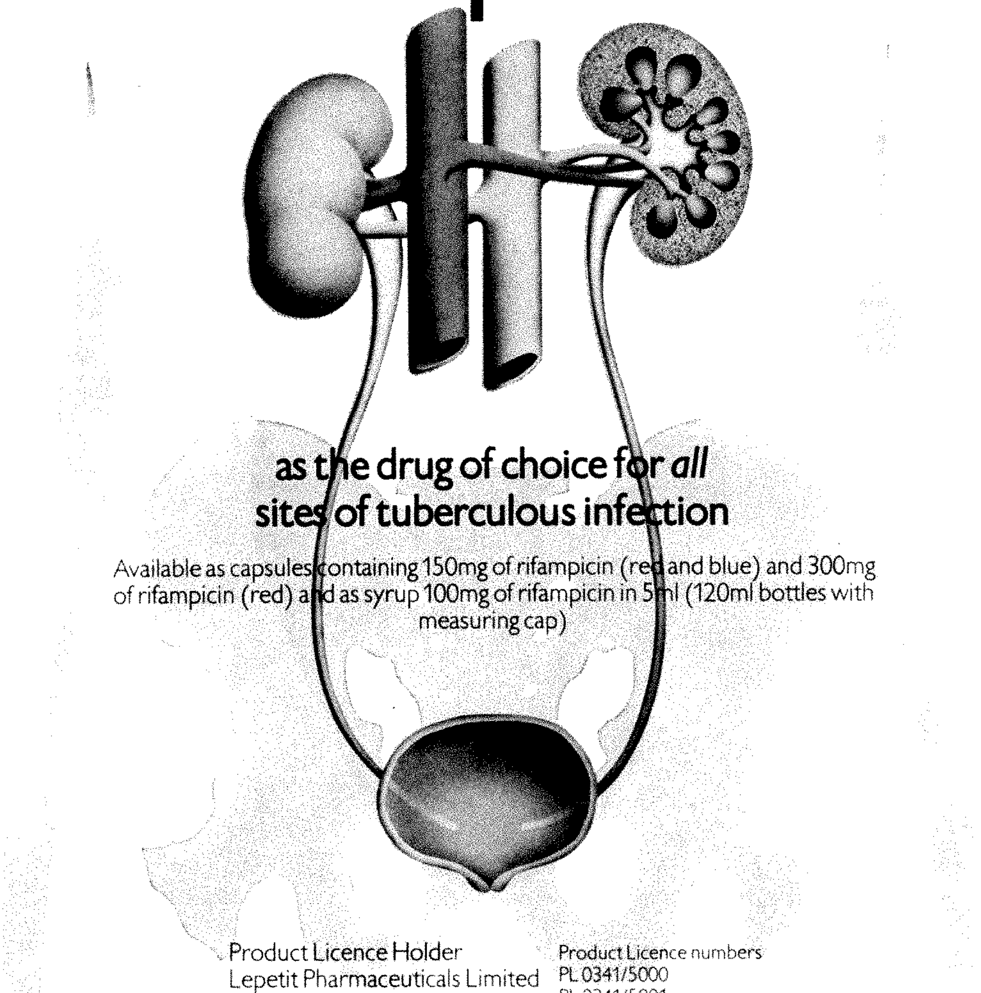

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Br. J. Dis. Chest (1979) *73*, 55

DIAGNOSTIC PNEUMOPERITONEUM

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Summary

Pneumoperitoneum as a diagnostic procedure has been practised for many years but there is a reluctance to make use of it. The author believes that this is due in some degree to lack of clearly defined indications and partly to lack of confidence in the safety of the procedure. In this paper the technique of diagnostic pneumoperitoneum is described and the risks are examined. Indications for its use are described. Finally, three case histories of special relevance are described and a summary of the results is tabulated with a view of giving an estimate of the diagnostic value which may be expected.

Introduction

Pneumoperitoneum was first described by German authors (Kelling 1902; Jacobaens 1912) for use in combination with laparoscopy and radiology. It subsequently became widely employed in the treatment of pulmonary tuberculosis. However, following the introduction of effective drug therapy it became obsolete as a therapeutic measure. Its use in the diagnosis of various abdominal conditions has been described (Maxfield & McIlwain 1942; Pietri & Massonat 1954; Lumsden & Truelove 1956; Stevens & McCort 1964), diaphragmatic shadows (Clay & Havlon 1950; Vaughn 1968), ruptures of the diaphragm (Bartley & Wickbom 1960; Ebert et al. 1967; Enge & Frysakes 1969; Christiansen et al. 1974), herniation through the foramen of Morgagni (Berger et al. 1962; Liguori & Eusanio 1971; Korobkin et al. 1973; Paris et al. 1973), hiatal hernias (Berry et al. 1955), eventration of diaphragm (Reed & Borden 1935; Bisgard 1946; Evans & Simpson 1950; Wynn Williams 1954; Lavender & Potts 1959; Michelson 1961), sequestration of lung (Hill et al. 1964) and inflammatory disease about the diaphragm (Asch 1966). Reed and Borden (1935) and Bartley and Wickbom (1960) described pneumoperitoneum as a valuable procedure more discussed than practised and other authors have voiced similar sentiments. Christiansen et al. (1974) describe several patients admitted to a department of thoracic surgery with undiagnosed rupture of the diaphragm and they advocate the 'old but infrequently applied procedure of diagnostic pneumoperitoneum'. Many papers describing the value of the procedure have been published between those of Reed and Borden (1935) and Christiansen et al. (1974) and yet despite its proven safety and value, pneumoperitoneum has failed to obtain general acceptance. In this paper the author describes his experience over a number of years and relates several case histories illustrating situations where it is likely to be of special value.

Materials and Methods

All patients were encountered during clinical practice as a physician in respiratory diseases and many patients with diaphragmatic conditions were referred after mass radiography.

Technique

The author performed pneumoperitoneum many hundreds of times during the period of its therapeutic use in pulmonary tuberculosis. The procedure is performed in the out-patient department. Various pneumothorax machines may be used. The author's preference is for the see-saw type such as that designed by Stott. The Saugman pneumothorax needle with its end-opening and stilette allows confirmation that the end of the needle is in the abdominal cavity. A satisfactory alternative may be the method described by Christiansen et al. (1974). The abdomen is first palpated to define any enlargement of liver or abnormal solid masses. Normally the site of injection is selected approximately 5–10 cm to the left of the umbilicus. Abdominal scars should be avoided and a history of generalized peritonitis is a contraindication. After infiltration with local anaesthetic the patient, lying supine, is instructed to make the abdominal wall tense by raising the head. The needle is then passed through the abdominal wall and usually penetration of the peritoneum can be felt. The stilette is then passed through the needle to confirm that the end of the needle is in the abdominal cavity; 20 ml of air are then instilled and a pause of 1 min allowed in the interest of absolute safety to ensure that there is no possibility of air having entered a vessel. A total of 600–800 ml is then instilled. The patient is instructed to regain the vertical position slowly to avoid the sudden shock of air coming up under the diaphragm. A postero-anterior and a lateral film are taken.

Stauffer et al. (1956) advocate the use of carbon dioxide on the grounds that it is safer than air because of greater rapidity of absorption. The value of this is questionable and the need for taking the films very quickly (before the carbon dioxide is absorbed) and the inability to take further views appear to offset any advantages.

There are a number of possible complications of induction of pneumoperitoneum. These are minor except for the important one of air embolism. It is difficult to assess the incidence of this because uncomplicated series are not usually reported. Of 53 published cases of embolism (Burman 1956), 14 were fatal and the majority of these were due to penetration of a solid organ (enlarged liver or spleen). All of these were instances of venous embolism and this type of embolism requires much larger amounts of air (100 ml or more; Sita-Lumsden & Elphinstone 1950) to be fatal than arterial embolism. Burman (1956) concluded that use of a pneumothorax apparatus of the see-saw type, e.g. Lillingstone–Pearson or Stott, will reduce risk because air can be injected only at low pressure. Another factor reducing risk was the use of a needle of the Saugman type with a terminal hole through which a stilette could be passed to confirm the position of the needle in the peritoneal cavity. Careful palpation of the abdomen to avoid solid organs and use of the lateral border of the left rectus are also important (Cafiero & Mastropaolo 1952). Puncture of hollow viscera is not very uncommon and does not usually give rise to ill effects (Stein 1951).

The author believes that observance of these precautions makes the possibility of complications remote. The only complication in the present series was a mild degree of preperitoneal surgical emphysema in one patient.

RESULTS AND DISCUSSION

Pneumoperitoneum was used for the investigation of 65 patients and the results are shown in Table I. A further patient (Case 3) is described as an example of the failure to make adequate use of this procedure. The majority were apparent eventrations (29), 2 of which were diaphragmatic hernias with prolapse of the liver which simulated eventration. Diaphragmatic shadows were due to pericardial cysts in 5 instances, diaphragmatic hernia in 7 and basal lung conditions in 5. Lacerations of the diaphragm were revealed in 2 of 6 suspected cases. Pneumoperitoneum was helpful in differentiating liver metastases

Table I. Pneumoperitoneum classified according to indications and diagnosis

Indication	*Number*	*Diagnosis*	*Number*
Apparent eventration or paralysis	33	Eventration	29
		Paralysis	2
		Diaphragmatic hernia	2
Diaphragmatic shadows	17	Pericardial cyst	5
		Diaphragmatic hernia	7
Suspected diaphragmatic injury	6	Basal lung consolidation or fluid	5
		Laceration of diaphragm	2
		Normal diaphragm	4
Abdominal conditions	9	Hepatomegaly due to metastases	3
		Hepatomegaly due to other conditions	2
		Subphrenic abscess	2
		Peritoneal adhesions	2
Total	65		

from other causes of liver enlargement in 3 of 5 patients and provided information in 4 patients with suspected subphrenic abscess.

The main value of pneumoperitoneum in apparent eventration is to differentiate it from diaphragmatic hernia, usually involving the liver or the spleen (Lavender & Potts 1959). The latter can closely mimic eventration with paralysis and paradoxical movement on sniffing but requires very different management. The same considerations apply to diaphragmatic paralysis without much displacement, discovered at routine examination. Differentiation between simple diaphragmatic paralysis and eventration with paralysis is discussed by Wynn Williams (1954). Reed and Borden (1935), surveying the literature, found that 165 of 183 reported cases involved the left side. Where there is an obvious cause of eventration or paralysis, e.g. carcinoma of the bronchus, pneumoperitoneum is not necessary. Case 3 is described as an example of failure to perform a pneumoperitoneum. He appeared to have eventration of the diaphragm with paralysis as demonstrated by radiographic screening but unfortunately did not have a pneumoperitoneum. He died 3 months later from the effects of herniation through the left diaphragm of the spleen and most of the stomach. A pneumoperitoneum performed on initial presentation 3 months before (as was the normal routine) would undoubtedly have demonstrated a diaphragmatic defect and enabled timely surgery to be performed. With the advantage of retrospection the lateral views of the diaphragm show a localized elevation, presumably due to prolapse of the upper pole of spleen, but it must be emphasized that there was no clue of a previous history of trauma to suggest that this was not a simple eventration. This case history (and others in this series) demonstrates how closely prolapse of liver or spleen through a diaphragmatic defect can mimic the paradoxical movement of diaphragmatic paralysis.

Pneumoperitoneum will demonstrate clearly whether a shadow at the lung base relates to an abdominal condition, e.g. diaphragmatic hernia or subphrenic abscess. Case 2 is an example of this use.

Traumatic rupture of the diaphragm resulting usually from a traffic accident is being reported in increasing numbers. Because of the frequency with which this injury was missed, Christiansen et al. (1974) advocated the use of pneumoperitoneum whenever physical examination or the chest radiograph after an accident was suspicious. In these patients air will pass into the pleural space from the pneumoperitoneum; Case 1 illustrates this. Investigation of a complaint of breathlessness some time after a road accident revealed apparent paralysis of the diaphragm through which the liver had prolapsed. Ebert et al. (1967) reported that 24 of 53 cases of traumatic rupture of the diaphragm were due to blunt trauma to the abdomen and in 22 of these 24 the left side was affected. This left-sided preponderance is similar to that in eventration of the diaphragm and in traumatic cases is presumably due to the protection of the presence of the liver on the right side.

Pneumoperitoneum can provide valuable information in the investigation of abdominal disease because of its ability to outline various organs, especially the liver and the spleen, and also the under surface of the diaphragm. Appropriate views are necessary, for example in studies of the liver surface, the lateral view with the patient supine is a valuable addition. Pietri and Massonat (1954) discuss the use of pneumoperitoneum in the study of cirrhosis of the liver. In the case of metastases, large swellings may be visible on the surface of the liver whereas in the case of cirrhosis the surface irregularity is much

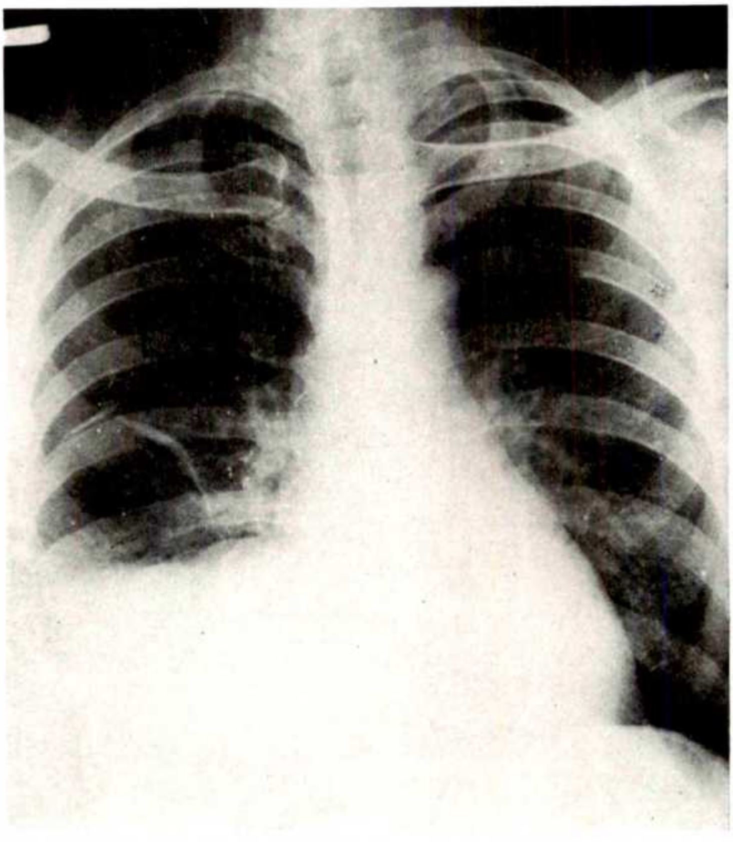

Fig. 1. Case 1. Elevation of the right diaphragm with indistinct outline

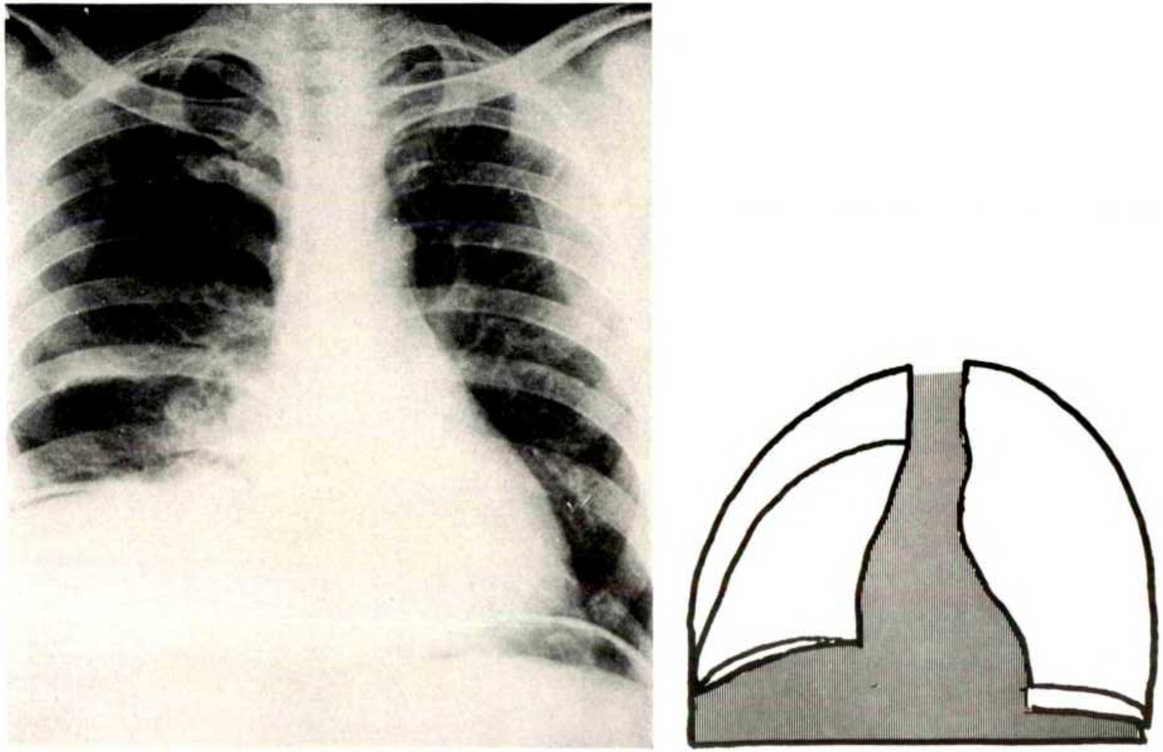

Fig. 2. Case 1. Pneumoperitoneum with penumothorax on the right side, demonstrating rupture of the diaphragm

finer. Pneumoperitoneum may provide valuable assistance in the diagnosis of subphrenic abscess. Where an abscess is present, no air will enter the upper right quadrant of the abdomen. If there are inflammatory changes at the right lung base only, air will outline the under surface of the right hemi-diaphragm.

Indications for pneumoperitoneum

These may be placed in four groups, as follows:

1. Shadows contiguous with the diaphragm, usually representing pneumonic consolidations, pericardial cysts, diaphragmatic hernias or tumours.
2. Apparent eventration or paralysis, especially to exclude diaphragmatic hernia.
3. After abdominal injuries where diaphragmatic damage may be suspected.
4. Abdominal diseases where outlining various organs by air may be of value.

Patients of Special Interest

Case 1 (32 years): traumatic diaphragmatic hernia

This patient complained of breathlessness on exertion which dated from a road accident 5 months previously. He had sustained fractures of the scapula and the pelvis and because of

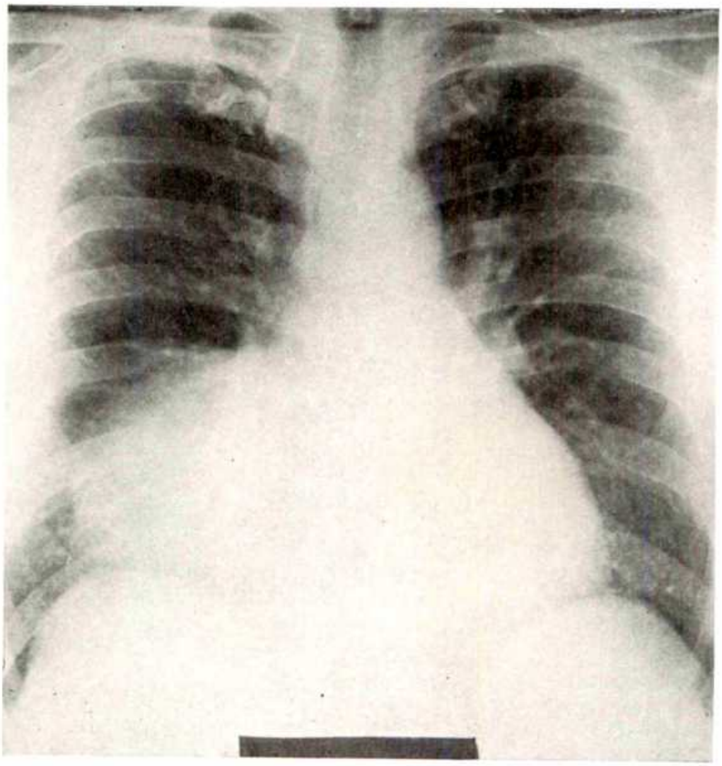

Fig. 3. Case 2. Shadow in the right cardiophrenic angle

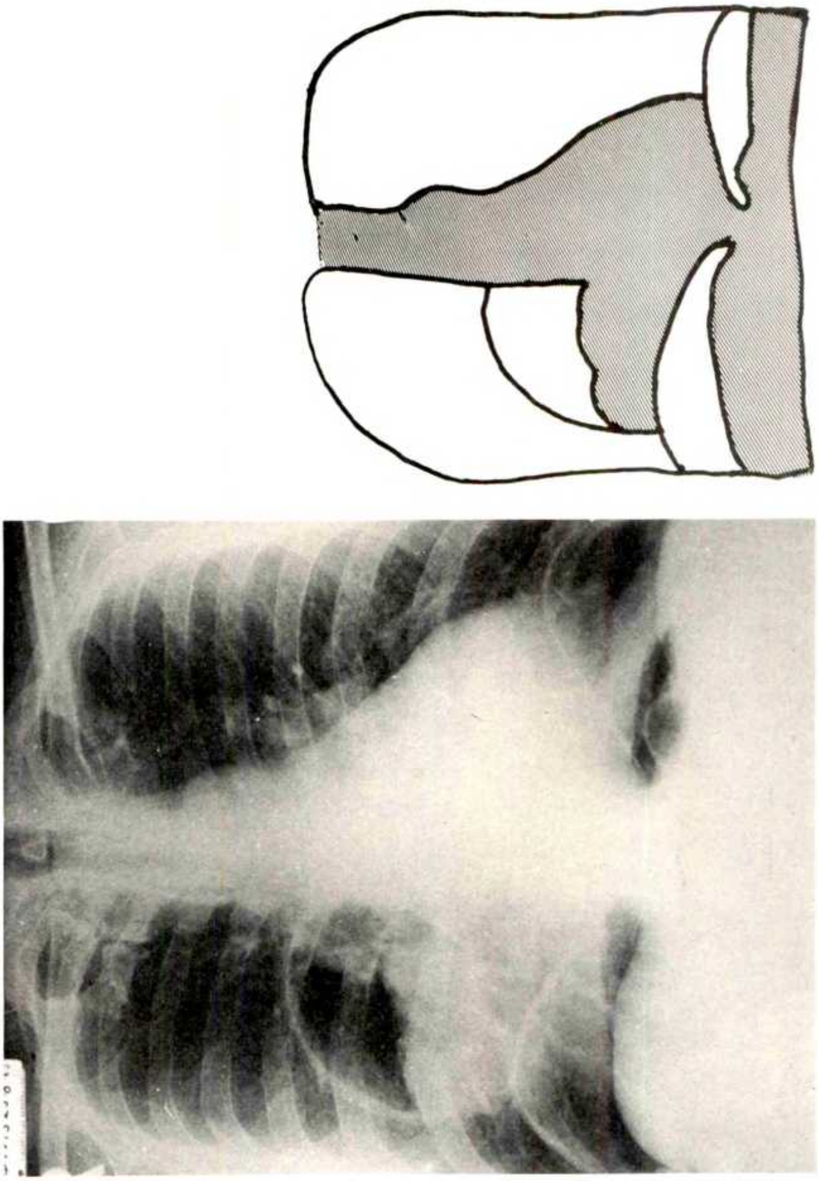

Fig. 4. Case 2. Pneumoperitoneum outlining a hernial sac containing a solid mass (omentum)

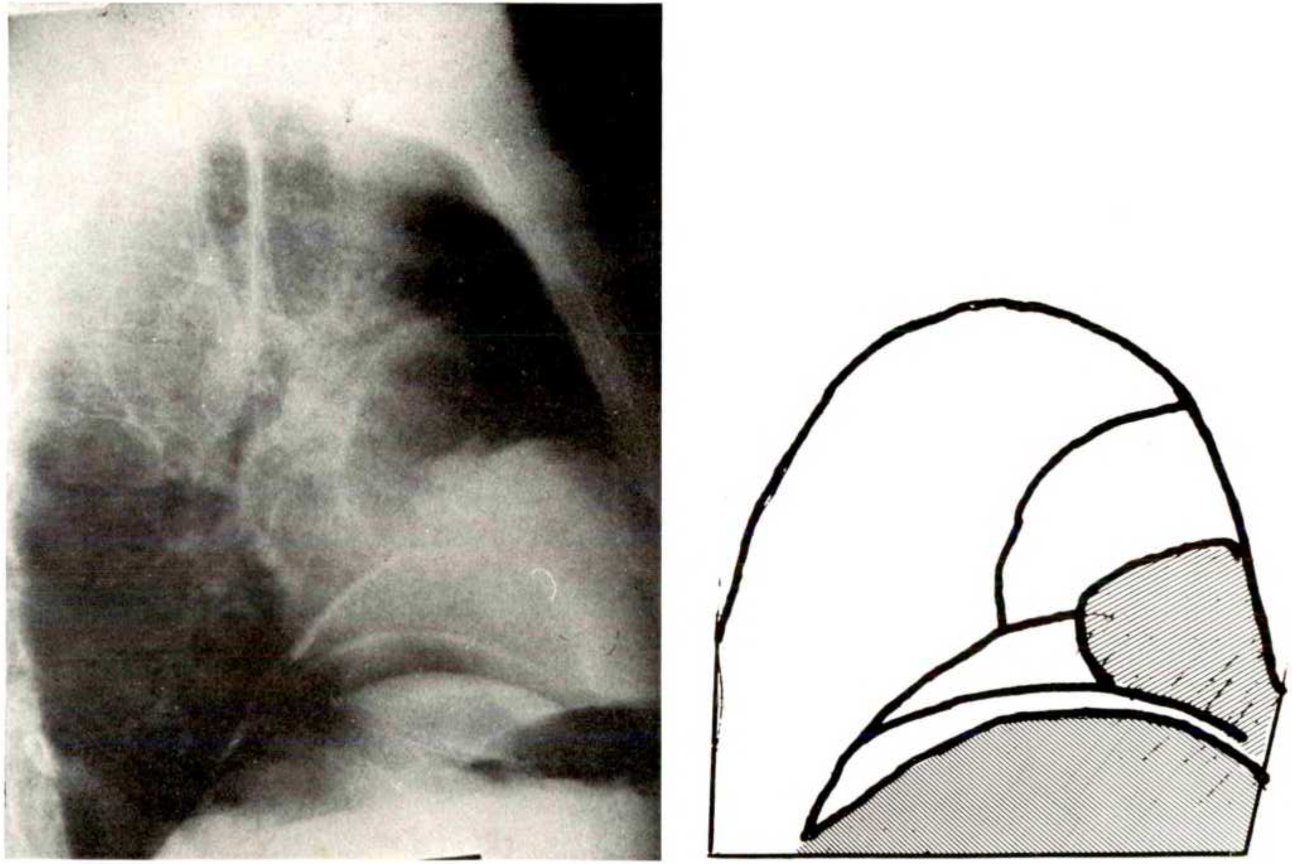

Fig. 5. Case 2. Pneumoperitoneum outlining a hernial sac containing a solid mass (omentum)

abdominal tenderness had a laparotomy but no perforation of a viscus was found. A subsequent chest radiograph revealed shadowing at the right base. He seemed to make a good recovery except for the breathlessness which was severe enough to prevent his return to work. On examination there was some impairment of percussion at the right base with reduction in breath sounds. A chest radiograph revealed a rather elevated right diaphragm with indistinct outline (Fig. 1). Radiographic screening showed paradoxical movement of the right hemi-diaphragm on sniffing, apparently the result of paralysis. Lung function tests demonstrated some impairment of ventilatory capacity without airway obstruction. Pneumoperitoneum was induced and revealed a pneumothorax (Fig. 2). The diaphragm was not paralysed but showed paradoxical movement on sniffing because of the movement of a prolapsed liver. At subsequent operation there was a large laceration of the diaphragm through which the liver had prolapsed. This was repaired. Subsequent progress was uneventful and he was able to return to work after a few weeks without breathlessness.

Comment: Laparotomy should have identified the diaphragmatic laceration but, failing this, only pneumoperitoneum could establish the nature of the abnormality.

Case 2 (53 years): hernia of Morgagni

This patient developed sudden pain in the right side of the chest while lifting a heavy weight. The pain persisted and 3 months later he was referred to hospital. He stated that he had always been aware of some breathlessness on exertion which had been worse during the preceding 3 months. Physical examination was negative but the chest radiograph (Fig. 3) revealed a large, round, dense, homogeneous shadow in the right cardiophrenic angle. The appearances suggested a pericardial cyst, diaphragmatic hernia or tumour as the most likely possibilities. A barium meal and follow through were normal. Pneumoperitoneum revealed a diaphragmatic hernia with the sac clearly outlined and containing a solid mass (Figs 4 and 5). Operation confirmed the large hernial sac protruding through the sinus of Morgagni and containing omentum. The sac was excised and the diaphragmatic hernia repaired with a good result.

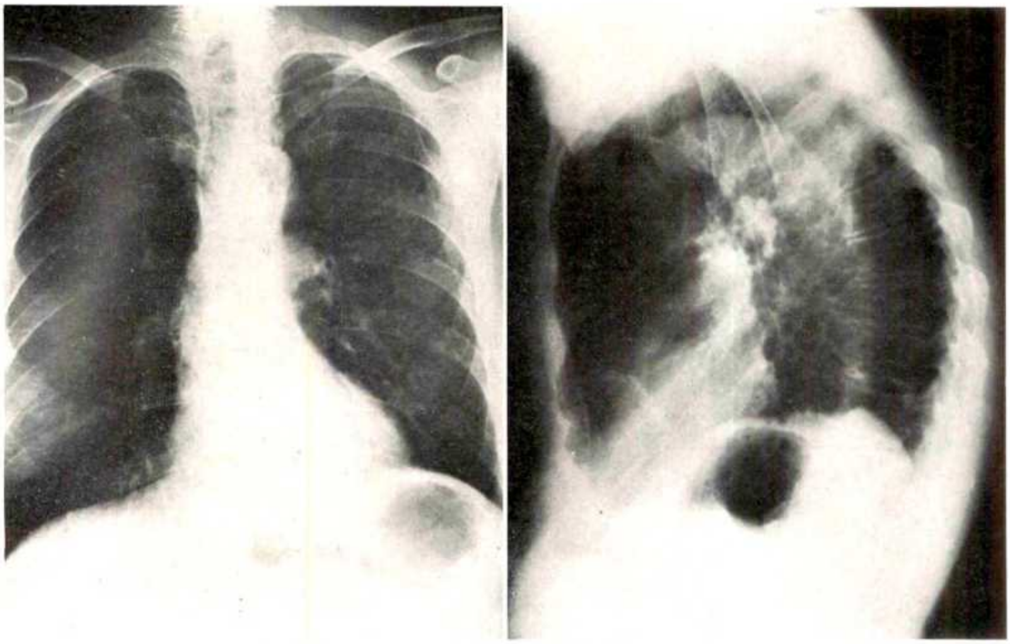

Fig. 6. Case 3. Elevation of the left hemidiaphragm

Comment: A barium meal will not reveal a diaphragmatic hernia if it does not contain bowel. In such cases a pneumoperitoneum is the only definitive investigation.

Case 3 (75 years): diaphragmatic hernia

This retired coal miner had a chest radiograph in July 1974 because of vague pains in the lower chest. The appearances then and at later radiographic screening were of an elevated and fully paralysed left hemi-diaphragm (Fig. 6). He was diagnosed as having eventration and for a number of reasons the usual pneumoperitoneum was not performed. In October of the same year he was admitted as an acute case with haematemesis and shock. A chest radiograph revealed herniation of stomach through the diaphragm (Fig. 7) but the patient died soon after admission. Necropsy confirmed the diaphragmatic hernia into which had passed the stomach, spleen, omentum and splenic flexure of large bowel. On review of this patient it was clear that on his first attendance the diaphragmatic tear was probably blocked by spleen and the condition was not distinguishable from eventration by radiographic means.

Comment: Simple diaphragmatic paralysis or eventration can be mimicked by a diaphragmatic hernia and routine pneumoperitoneum is the only certain way of avoiding this mistake.

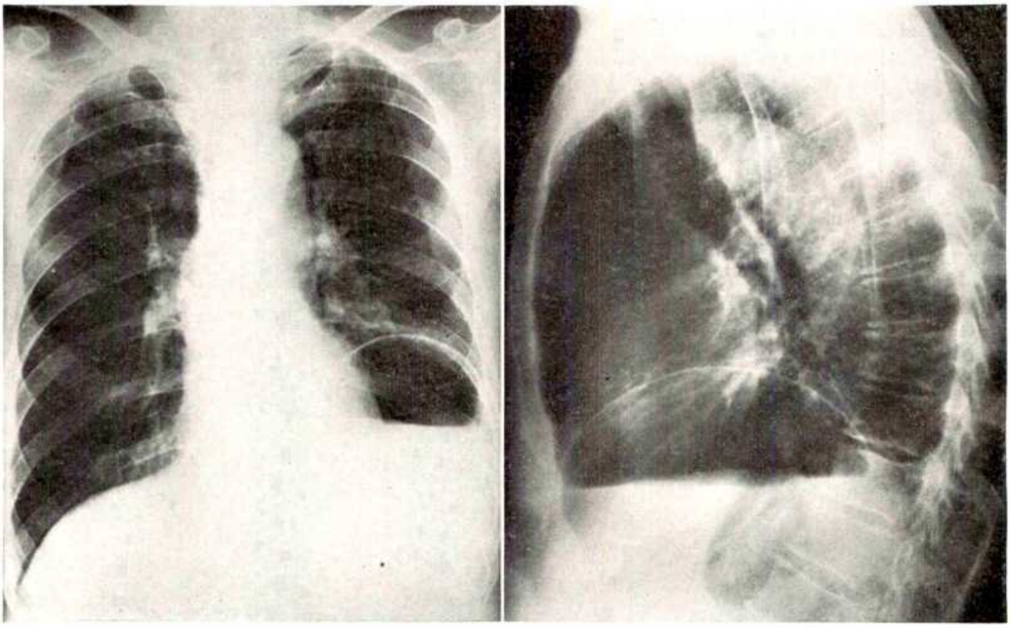

Fig. 7. Case 3. Herniation of the stomach through the left diaphragm

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METABOLIC STUDIES IN ACUTE ASTHMA BEFORE AND AFTER TREATMENT

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Summary

We studied the metabolism and hormone profile of 9 patients with moderately severe acute asthma before treatment, and again 10 min after intravenous aminophylline (250 mg) or the selective beta-adrenergic stimulant hexoprenaline (5 μg) intravenously. Compared with basal values in normal subjects, the untreated asthmatics had statistically significant raised mean plasma pancreatic glucagon, free fatty acid (FFA) and glucose levels in the plasma and a significantly depressed mean plasma potassium level. Insulin, growth hormone, cortisol, thyrotropin and ketone body levels were normal. The only significant changes after therapy were a further fall in plasma potassium in the hexoprenaline-treated patients and a rise in the mean lactate concentration of the group as a whole. The clinical implications of these findings are briefly considered.

INTRODUCTION

In a previous paper we have demonstrated several metabolic alterations after selective beta-adrenergic stimulation in healthy subjects, the most striking being a rise in plasma free fatty acid (FFA) levels (Goldberg et al. 1975). It is therefore seemed pertinent to extend these studies to asthmatic patients in acute exacerbation. In addition, it gave us an opportunity of examining the biochemical findings in the plasma of acute asthmatics before therapy. Apart from reports of elevated FFA concentrations in mild chronic bronchial asthma (Neville et al. 1977) and in acute asthma unresponsive to the usual treatment (Tickner et al. 1977), no comprehensive metabolic study has been attempted in acute bronchial asthma.

Patients and Methods

We studied 9 untreated patients (7 women and 2 men), aged 20–51 years, with moderately severe acute asthma. Six of the patients were newly diagnosed and previously untreated while the other 3 were known cases who had not taken any medication for at least 7 days. All were within 15% of ideal body weight (Metropolitan Life Tables 1959). None showed clinical evidence of respiratory tract infection. Seven gave a history consistent with atopy or atopic disorders.

All patients were examined and special note made of the pulse rate, blood pressure, degree of pulsus paradoxus, presence of cyanosis and peak flow rate (Wright Peak Flow Meter). The patients were studied between 3.5 and 14 hours (mean 6.5 hours) after their last meal.

An intravenous cannula was inserted in the antecubital vein and kept open by a slow saline infusion. A pretreatment heparinized venous blood sample was collected and kept in ice. Samples for lactate and ketone measurements were put into ice-cold perchlorate, and one for glucagon estimation into tubes containing aprotinin. An arterial sample was also taken for blood gas and pH analysis. Five patients were then treated with 250 mg aminophylline and the other 4 with 5 μg of the selective (beta$_2$) adrenergic stimulant, hexoprenaline (Benjamin & Van As 1972), each given intravenously over 5 min. All but 1 had a satisfactory clinical response. After 10 min another venous sample was taken and handled as before. All samples were then centrifuged immediately and deep frozen at −20°C. Aliquots of plasma were taken for measurement of FFA (Dole 1956), insulin (Heding 1972), pancreatic glucagon (Heding 1971), growth hormone (Hartog et al. 1964), lactate (Bergmeyer 1974), ketones (Bergmeyer & Bernt 1965), glucose (Auto Analyser), potassium (Auto Analyser), thyrotropin (Odell et al. 1965) and cortisol (Fiorelli et al. 1972). Twenty-four healthy young non-obese subjects served as controls for the insulin and glucagon data, and a smaller group of 10 subjects for the other biochemical measurements.

Paired and unpaired *t*-tests, whichever was applicable, were used for the statistical analyses.

The study was approved by the Human Research Committee of the University of the Witwatersrand.

RESULTS

Table I summarizes the salient clinical data in the 9 patients before treatment. All showed reduced peak flow, increase in the degree of pulses paradoxus, and hypoxaemia. Their $P\text{aco}_2$ levels were low to usual. These features, together with the uniformly detected physical signs of hyperinflation and wheezing, were consistent with an acute attack of asthma.

Table I. Details of clinical findings in 9 patients with acute asthma (mean and range)

Pulse rate (beats/min)	103 (90–120)
Pulsus paradoxicus (mmHg)	24 (15–40)
Peak flow (litres/min)	116 (80–160)
$P\text{ao}_2$ (mmHg)	57 (47–65)
$P\text{aco}_2$ (mmHg)	34 (29–39)

Pretreatment metabolic findings (Table II)

The untreated asthmatics had significantly elevated mean plasma glucose, FFA and pancreatic glucagon concentrations compared with fasting controls. The elevated FFA

Table II. The hormonal and metabolic profile mean ±SEM of patients with acute bronchospasm

	Asthmatics			*Fasting controls*	*P*
	No.	Pre-treatment	Post-treatment		
Glucose (mg/dl)	9	94±4.3	97±3.6	81±2.1	<0.05†
Lactate (mg/dl)	9	11.6±1.5	14.2±1.5	9.4±0.8	<0.05*
FFA (μEq/litre)	9	675±49	700±17	497±20	<0.005†
Glucagon (ng/ml)	8	0.37±0.03	0.38±0.04	0.19±0.01	<0.0005†
Insulin (μU/ml)	8	8.9±2.6	13.5±3.8	7.4±0.9	
K (mmol/litre)	8	3.8±0.18	3.6±0.22	4.4±0.15	<0.025†
K (mmol/litre) (hexoprenaline group only)	4	3.8±0.2	3.4±0.3		<0.01*

* Pre *vs.* post-treatment (paired *t*-test).

† Pre *vs.* fasting controls (unpaired *t*-test).

levels were not significantly correlated with corresponding glucagon, cortisol, insulin or growth hormone responses. Their mean plasma potassium level was significantly depressed. Insulin, growth hormone, cortisol, thyrotropin and ketone body concentrations were all within the normal fasting range.

Effects of therapy (Table II)

Potassium levels fell further in the hexoprenaline-treated group only; the fall in potassium was not significantly correlated with insulin or cortisol levels. There was a modest, but significant, rise in the mean lactate concentration of the group as a whole. No other significant metabolic or hormonal changes were noted after treatment.

Clinically all but one of the patients responded well; airway narrowing decreased markedly as indicated by an increase in peak flow ($\geqslant 40\%$) which was observed in those instances where it was remeasured. The mean pulse rate was unchanged from the pre-treatment rate of 103 beats/min to the post-treatment rate of 106 beats/min.

DISCUSSION

These metabolic features of acute asthmatics not receiving medication and their response to therapy has not previously been reported. Our study confirms the finding of raised FFA concentrations in asthmatics (Neville et al. 1977; Tickner et al. 1977). This occurs in other stressful situations (Allison et al. 1968; Taggart & Carruthers 1971; Vetter et al. 1974) and is probably due to the stress of the asthmatic attack itself (Tickner et al. 1977). The *magnitude* of FFA elevation is, however, less marked than reported after myocardial infarction for example (Vetter et al. 1974), and may be due to the fact that several hours had elapsed before presentation. Administration of selective beta-adrenergic stimulants and aminophylline is known to raise FFA levels in healthy subjects (Atuk et al. 1967; Goldberg et al. 1975), but this was not apparent in our patients given these two forms of therapy. Tickner et al. (1977) have also recently reported insignificant FFA rises after treating asthmatics with salbutamol. The explanation might, in part, be related to such factors as the already stimulated FFA concentrations before therapy and the relief of distress by therapy. A further intriguing possibility is the existence of an intrinsic defect of the beta-adrenoreceptor in asthmatics (Szentivanyi 1968) so that the metabolic effects of beta-adrenergic stimulation are inherently blunted.

The hyperglucagonaemia observed in the untreated patients is of interest. It also presumably reflects catecholamine stimulation of pancreatic alpha cells by the stress, since this is an important mechanism for augmenting glucagon secretion (Unger 1974). Insulin levels should have been reciprocally suppressed, however, and our data did not show this. Despite the elevated glucagon and FFA levels it is noteworthy that substantial hyperketonaemia was not observed. Potassium levels fell in the four hexoprenaline-treated patients. Beta-adrenergic stimulants promote the entry of potassium into cells both in vitro (Gardner et al. 1975) and in animal experiments (Guthrie & Murphy 1975), and salbutamol helps in the treatment of hyperkalaemic periodic paralysis (Wang & Clausen 1976).

Clinically this study provides further reasons for caution in the use of parenteral beta-adrenergic stimulants in asthma (Goldberg et al. 1975; *British Medical Journal*, 1975). Their selectivity is relative and all may stimulate cardiac beta$_1$ receptors. In the presence of hypokalaemia, hypoxia and possibly high FFA levels (Oliver 1972), these agents are therefore potential disturbers of cardiac rhythm. Myocardial necrosis is a possibility: it has recently been reported in an asthmatic patient treated with intravenous salbutamol and aminophylline (Szczeklik et al. 1977).

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ADDENDUM

Since the preparation of this paper, a related study has appeared (Nogrady et al. 1977). This has also demonstrated a fall in the plasma potassium levels after therapy and no change in insulin, although the plasma free fatty acid level rose further after salbutamol infusion.

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THE DIAGNOSIS OF PULMONARY CARCINOID TUMOURS

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Summary

Carcinoid tumours of the lung are commonly misdiagnosed as carcinoma and even if they are recognized their behaviour may be unexpected. In a series of ten cases which had caused diagnostic difficulty there had been an incorrect interpretation of bronchial biopsy material in four, of the resected tumours in another four, of a needle biopsy core in one and of autopsy material in another. In some cases these errors led to needless radiotherapy and to an unnecessarily poor prognosis being given. In all cases the diagnosis of carcinoid tumour was made retrospectively by the demonstration of argyrophil granules in the tumour cells or by electron microscopy. Electron-dense bodies could be found in material that had been fixed in formol saline or even embedded in paraffin so that this method may be used retrospectively. Two of these ten tumours behaved in a malignant fashion but progressed much more slowly than most samples of bronchial carcinoma. The possibility of carcinoid tumour should be considered in any patient with a tumour of the lung who is unusually young, or who is a non-smoker or where bone or calcification are present in the tumour. It is also suggested that unrecognized cases of carcinoid tumour may be found amongst long-term survivors with lung tumours which have been treated by radiotherapy or chemotherapy without surgery.

INTRODUCTION

Bronchial carcinoid tumours grow slowly and can usually be cured by surgery. For these reasons their recognition is important, but because of their very variable histological appearance they sometimes go unrecognized and are misdiagnosed as carcinomas. A number of papers on both carcinoids and carcinomas of the lung refer to this difficulty and give instances where the original opinion of the pathologist had been incorrect or equivocal (Jackson & Konzelman 1941; Goodner et al. 1961; Zellos 1962; Markel et al. 1964; Smith 1969; O'Grady et al. 1970; Burcharth & Axelsson 1973; Lawson et al. 1975; Paulson & Reisch 1976). This paper reviews the significant pathological findings in ten cases of carcinoid tumour which had all given rise to diagnostic difficulties from the pathologists' point of view. Nine had been diagnosed as carcinomas and this sometimes led to quite inappropriate therapy. Several features could be identified which might have suggested the true nature of the tumour at the time of the original error of interpretation.

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Materials and Methods

These cases came to the author's attention when review of the material was requested by the clinicians or was carried out for some other reason. The pathological material available consisted of paraffin blocks in all cases apart from Case 9 from which tissue stored in formol saline was also examined. The material was derived from a number of different institutions in south Yorkshire.

Fresh paraffin sections were stained with haematoxylin and eosin, and impregnated with silver by the Masson Fontana and Bodian protargol methods (Bodian 1936). The diazo coupling reaction was carried out (Culling 1974) and the presence of mucin was sought using the alcian blue–PAS sequence of Mowry (1956). Electron microscopy was carried out in two cases using formalin-fixed material in Case 9 and paraffin-embedded material in Case 10. These were re-processed for plastic embedding by the method of Rowden and Lewis (1974) as modified by Norris (Kennedy 1977). The clinical records were also reviewed for details of the subjects' ages and smoking histories.

Only material obtained by bronchial biopsy was available in four cases. In four cases pneumonectomy or lobectomy had been carried out. In Case 8, material obtained at necropsy was available in addition to the previous bronchial biopsy. In Case 9 a percutaneous needle biopsy had been performed before lobectomy.

CLINICAL FEATURES

The significant clinical features are summarized in Table I.

The sexes are equally represented and the average age at the time of biopsy was 48 years. Four patients were under 40 years of age and the youngest was only 21. Of the nine patients whose smoking habits were known, five were recorded as being non-smokers. It may be concluded that, compared with cases of lung cancer, there were more females and more non-smokers than would be expected. As a result of misdiagnosis, five were referred for radio-therapy, but this was withheld in Case 10 when the reviewing pathologist recognized the true nature of the tumour.

Four patients died, but in three of these (Cases 2, 3 and 8) there was no evidence to implicate carcinoid tumour in their deaths. In Case 2, there was no evidence of a thoracic tumour at the time of her death, which was thought to be due to a pelvic malignancy. In Case 3, removal of the irradiated lung became essential due to recurrent episodes of infection and it was at this time that the original error was discovered. The patient lived for a further 23 years without developing evidence of recurrence or metastases. In Case 8, death was almost certainly due to the metabolic effects of uncontrolled diabetes mellitus; the patient was a tramp who persistently refused to comply with his prescribed diet. A pathologist's conclusions were that death was due to 'pancreatitis, acromegaly, pituitary infarct and bronchogenic carcinoma'. However, the tumour was no larger than it had been judged to be radiologically on previous occasions and there was no secondary deposit even though the tumour had been present for at least three years. Cases 4 and 7 are examples of malignant carcinoids as judged by their behaviour, but even in these malignant tumours progress was slower than in bronchial carcinoma so that the diagnosis of carcinoid would have been worth making from the point of view of giving a correct prognosis.

PATHOLOGICAL FINDINGS

The pathological findings are summarized in Table II.

Table I. Clinical features of ten pulmonary carcinoids

Case no.	*Age and sex*	*Smoking history*	*Original pathological diagnosis*	*Other clinical features*	*Treatment*	*Survival*
1	M,52	14/day	Carcinoma	18 months history	Biopsy only	Alive 11 years later with proven coelic disease
2	F,63	Non-smoker	Undifferentiated carcinoma	Collapse of right upper lobe	Radiotherapy	Died 3 years after biopsy with pelvic tumour. No evidence of recurrence in chest
3	F,34	Not known	Adenocarcinoma	Inoperable	Radiotherapy. Lung removed 2 years later	Survived 25 years after diagnosis without evidence of recurrence
4	F,60	Non-smoker	Carcinoma	Incidental finding on chest X-ray	Segmental resection. Radiotherapy	Died 7 years after operation. Sclerotic secondaries in spine and pelvis
5	M,31	Non-smoker	Undifferentiated carcinoma	Recurrent chest infections for 10 months	Lobectomy	Alive 6 months later. Lost to follow-up
6	F,21	Non-smoker	Adenocarcinoma	—	Pneumonectomy	Alive 27 years later
7	M,60	Ex-smoker (20/day)	Carcinoma mimicking carcinoid	Haemoptysis. Multicentric tumour	Two lobectomies and radiotherapy	Alive 12 years after original operation and 6 years after recurrence.
8	M,37	10–19/day	Carcinoma	Acromegaly. Diabetes mellitus	Biopsy only	Died of diabetic coma 15 months after biopsy
9	F,67	Non-smoker	Carcinoma	—	Lobectomy	Alive 3 years later
10	M,57	'Heavy smoker'	Not established	Collapse of right lower lobe	Biopsy only	Alive 15 months after diagnosis

Table II. Pathological features of ten pulmonary carcinoids

Case No.	*Source of material*	*Site of tumour*	*Lymph node involvement*	*Histological pattern*	*Argyrophilia*	*Mucin*	*Other features*
1	Bronchial biopsy	Central, left lower lobe		A B	+	—	Inoperable
2	Bronchial biopsy	Central, right upper lobe		A B C	+	—	
3	Bronchial biopsy	Central, left main bronchus		B	+	—	
4	Lobectomy	Central, left upper lobe	—	A B C	+	+	
5	Lobectomy	Central, right lower lobe	—	A B	+	+	
6	Pneumonectomy	Central right lower lobe	—	A B	+	—	Bone present
7	Two lobectomies	Central, main bronchi	+	A B C	+	+	Multicentric
8	Bronchial biopsy. Necropsy	Central, right upper lobe	—	A B	+	—	Inoperable. Partly calcified
9	Needle biopsy	Peripheral, right middle lobe	—	B C D		—	Dense core bodies
10	Bronchial biopsy	Central		B D		—	Dense core bodies. Inoperable

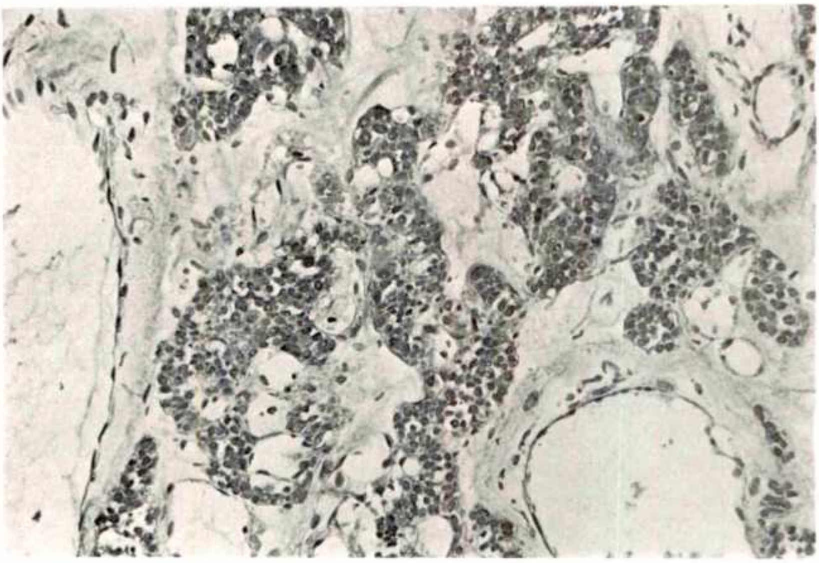

Fig. 1. Case 1. Bronchial biopsy. The tumour forms solid acini and ribbons in a vascular fibrous stroma. H & E ×195

One tumour (Case 7) was a malignant carcinoid on pathological grounds alone in that lymph node metastases occurred and the tumour was both multicentric and recurrent. Soga and Tazawa (1971) classified carcinoid tumours into four main groups on histological grounds. Their group A consists of tumours of the classical nodular configuration as seen in midgut carcinoids. Type B includes tumours with trabecular or ribbon-like

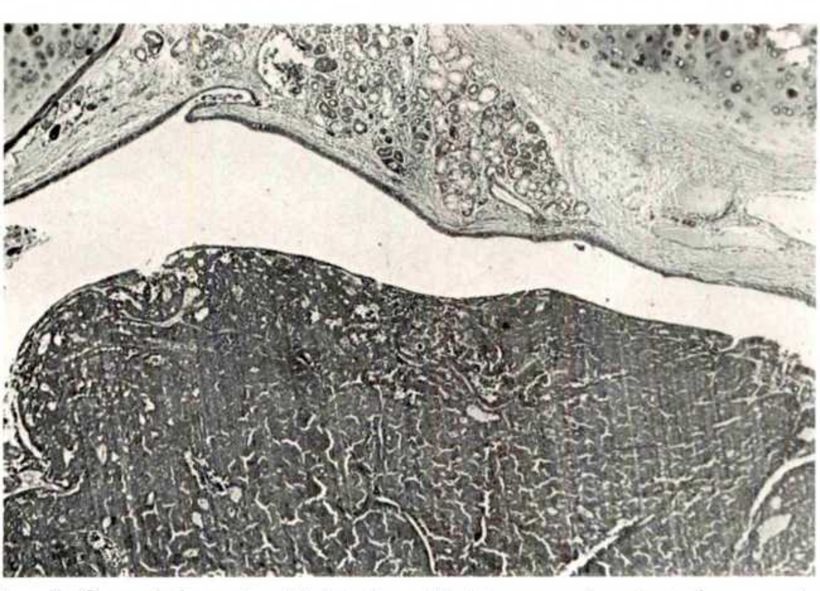

Fig. 2. Case 7. One of the polypoid intrabronchial tumours found at the second resection. This man had multicentric tumours in the left lung. An upper lobectomy was carried out in 1966 and the lower lobe was removed 6 years later. H & E ×30

patterns and is particularly common in tumours of foregut origin (Fig. 1). Type C has tubular or acinar formations while type D is atypical. In the present small series the tumours were of mixed pattern but the predominant form was type B, the variety usually found in carcinoids originating in the foregut. Only three tumours had areas of the classical type A formation, which is the familiar pattern of carcinoid tumour and this is, perhaps, the reason why the possibility of carcinoid tumour was not considered in the first instance. The two malignant carcinoids contained type C areas and had a glandular pattern, but this histological variety is not necessarily malignant (Fig. 2). The diazo reaction was positive in only one case. None of the tumours were argentaffin but argyrophilia was found in all of the eight cases in which it could be attempted (Fig. 3). Mucin was present in one case and bone or calcification was prominent in two.

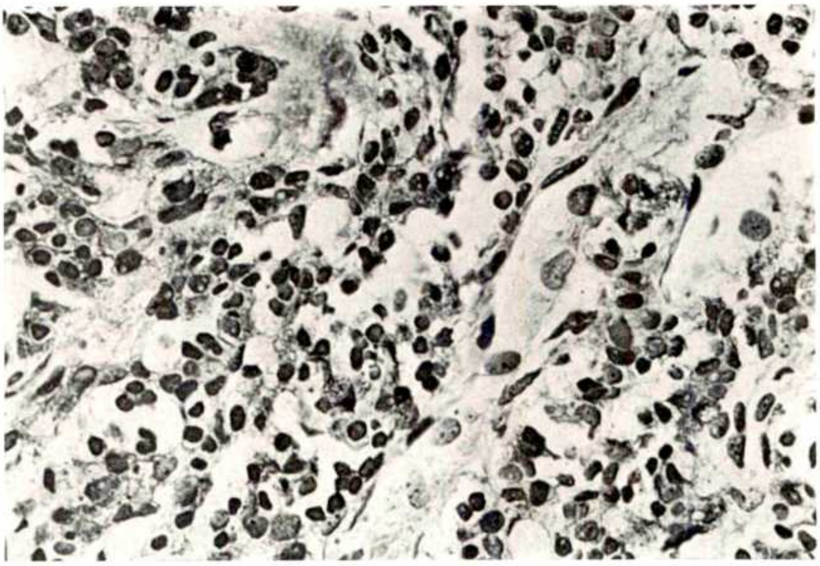

Fig. 3. Case 1. A higher magnification of the tumour shown in Fig. 1. Dark argyrophilic granules are present in the cytoplasm of the tumour cells. Bodian's protargol ×480

DISCUSSION

Due to erroneous interpretation of their pathological specimens, all these patients had been considered to have bronchial carcinoma at some stage of their illnesses. As there is no evidence to connect bronchial carcinoids with cigarette-smoking, it is suggested that a diagnosis of bronchial carcinoma should always be reconsidered in any patient who is a non-smoker or who is under the age of 40 years. The application of such criteria might have prevented error in seven of the patients in this series. In two of these cases this suspicion might also have been aroused by the presence of calcification or bone in the tumour (Delarue 1951; Thomas & Morgan 1958; Salyer et al. 1975), features which are very unusual in bronchial carcinoma (Fig. 4).

The co-existence of acromegaly with a tumour of the lung is highly suggestive of the possibility of carcinoid tumour (Sonksen et al. 1976) and in Case 8 it is remarkable that there were three features which could have indicated the correct diagnosis; the patient was young, he was acromegalic and the tumour was partly calcified.

If the possibility of carcinoid tumour is considered in all cases with such unusual features then the admittedly variable histological patterns of carcinoid tumour are more likely to be recognized and errors avoided. The Masson Fontana and diazo techniques have little to offer by way of information as they are usually, but not always, negative. Argyrophilia is worth seeking for it was found in most of the present series. Unfortunately, this is not always the case and many bronchial carcinoids are not argyrophilic (Soga & Tazawa 1971). Furthermore, the techniques for detecting argyrophilia are not particularly easy or reproducible and may give different results in different hands.

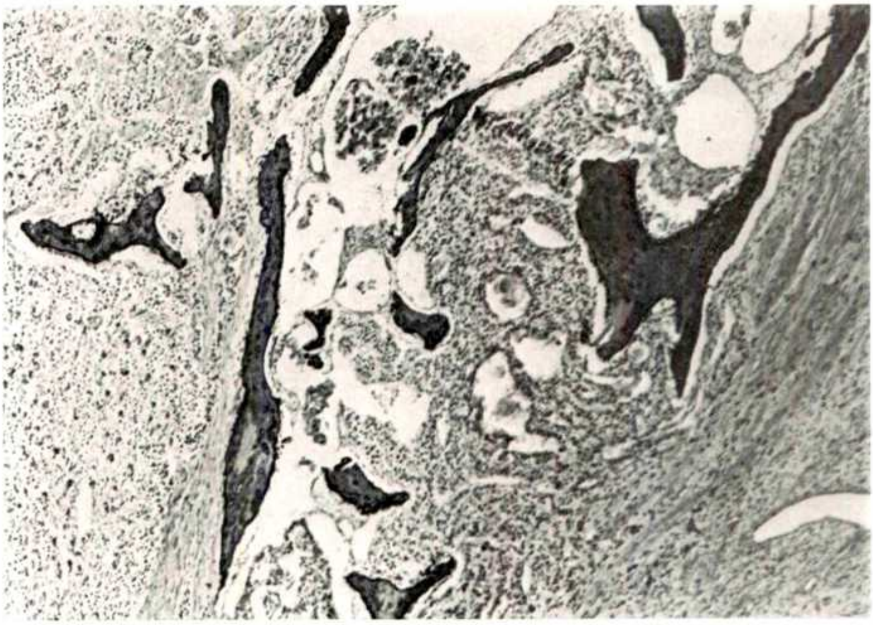

Fig. 4. Case 6. Female aged 44. Bone formation within the tumour. Bodian's protargol × 40

Cases 9 and 10 illustrate the value of electron microscopy in these cases, for the demonstration of electron-dense bodies provides objective evidence to support the diagnosis of carcinoid tumour. These bodies are also present in oat cell carcinoma (Bensch et al. 1968) but only in small numbers compared with carcinoids in which they are more abundant (Bensch et al. 1965; Toker 1966; Gmelich et al. 1967). The danger of failing to distinguish between carcinoid tumour and oat cell carcinoma is real, for a number of authors have stated that some long-term survivors, who had been regarded as having oat cell carcinoma, eventually proved to have atypical carcinoids (Zellos 1962; Markel et al. 1964; O'Grady et al. 1970; Burcharth & Axelsson 1973; Lawson et al. 1973; Paulson & Reisch 1976). As shown in Figs 5 and 6, the presence of electron-dense bodies can be established in both formalin-fixed and paraffin-embedded material (Salyer et al. 1975; Soga & Tazawa 1971). These organelles are very durable and the ability to recognize them in such unpromising material enables the diagnosis of carcinoid to be made in retrospect.

Four of the patients in this series received radiotherapy. In one (Case 3), this was definitely harmful, for the lung was rendered useless and the patient survived for many years after the lung with its irradiated tumour had to be removed because of sepsis.

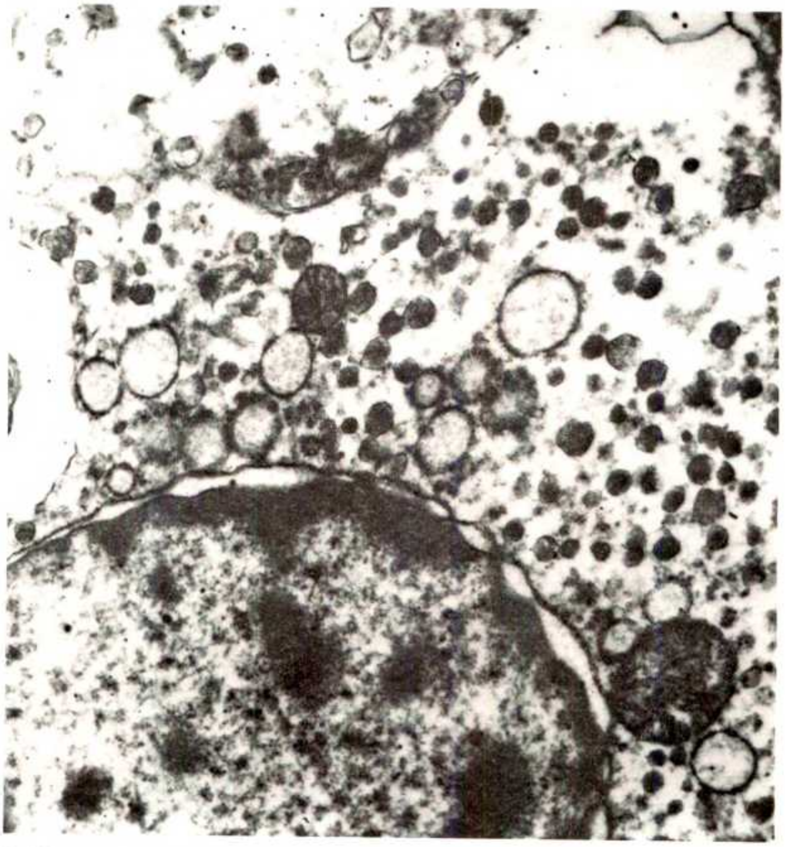

Fig. 5. Case 9. Electron micrograph of material selected from the lobectomy specimen which had been fixed by perfusing the bronchial tree with formol saline. The preservation is poor but dense core bodies are clearly identifiable. Uranyl acetate–lead citrate × 20 000

Radiotherapy was used in combination with surgery in both the cases of malignant carcinoid (Cases 4 and 7), but there is no clear evidence that it conferred any benefit. Its value in Case 3 cannot be assessed because of lack of information. In cases of bronchial carcinoid, which is a tumour of only limited malignant potential, surgery seems to offer the prospect of complete cure without the hazards of leaving damaged lung as in Case 3. Apart from being the most rational treatment for a tumour of low malignancy, surgery has the secondary advantage of providing the pathologist with the entire tumour so that the diagnosis may be established beyond doubt.

Many of the patients diagnosed as having an oat cell carcinoma on bronchial biopsy may be treated with radiotherapy alone as this is claimed to give the least unsatisfactory results (Fox & Scadding 1973). Herein lies a danger, for if a carcinoid tumour is inadvertently labelled as an oat cell carcinoma, some years may go by before the error is realized (Cases 2, 3 and 4); even if the carcinoid is of the malignant type its rate of growth will be much slower than that of an oat cell carcinoma. A review of all long-term survivors of radiotherapy or chemotherapy might reveal more unsuspected cases of bronchial carcinoid tumour.

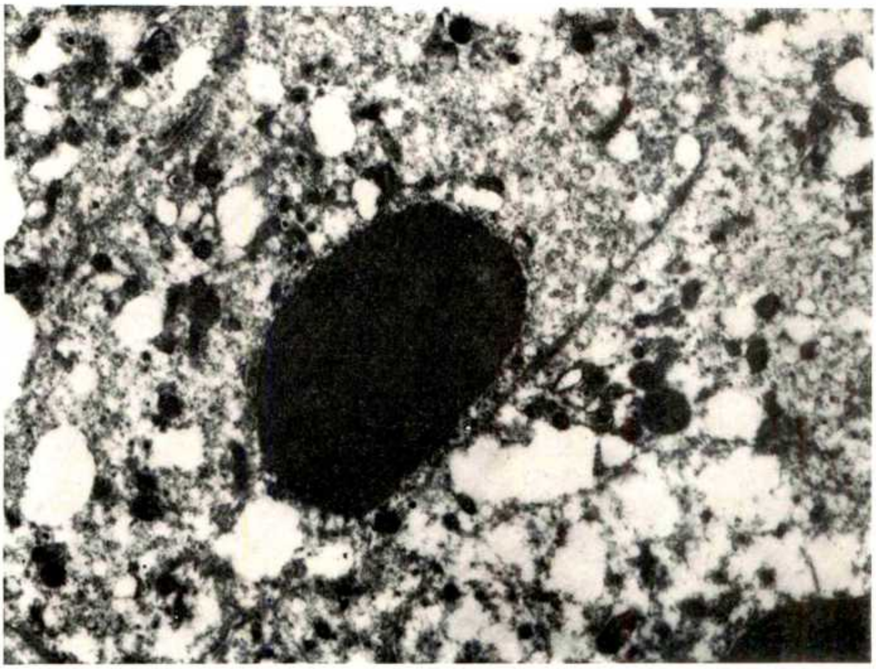

Fig. 6. Case 10. Part of a paraffin-embedded bronchial biopsy specimen which was cut out of the paraffin block and re-processed for electron microscopy. The nucleus of a cell appears as a dark ovoid mass and few organelles are identifiable but small electron-dense bodies have survived the processing. Uranyl acetate–lead citrate × 7100 (*By courtesy of Dr I. A. Carr*)

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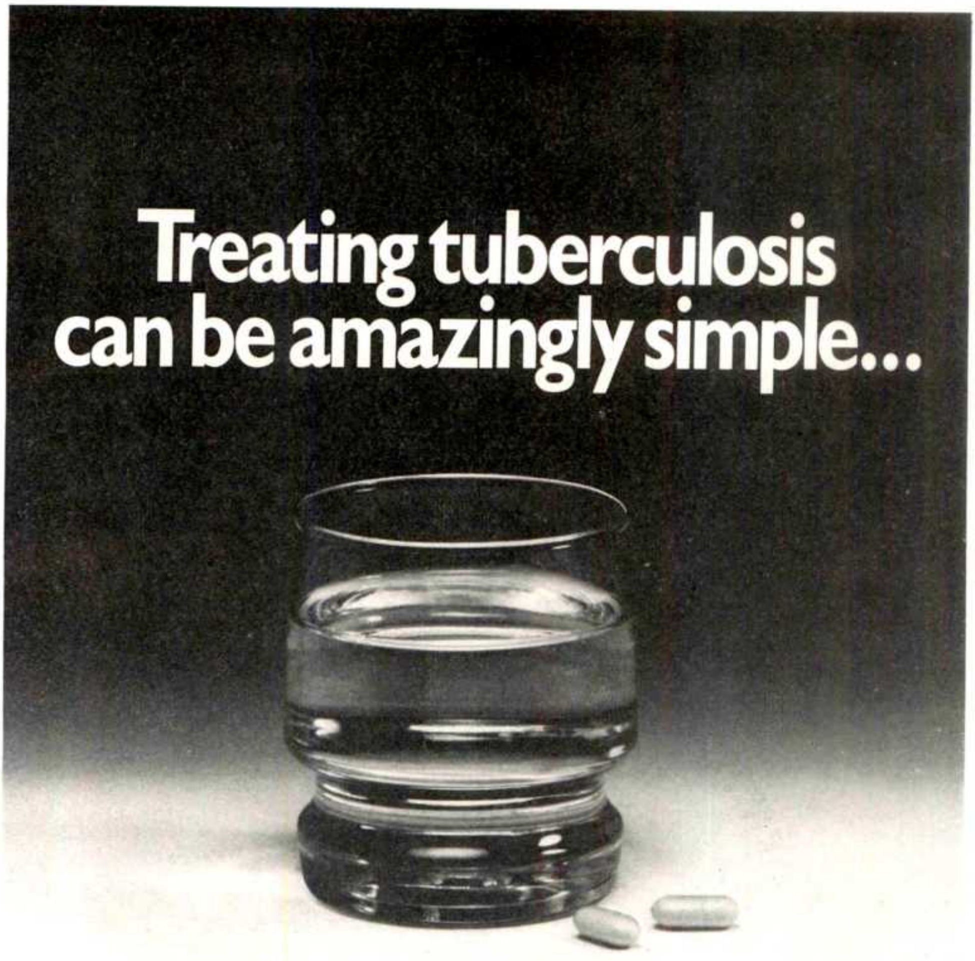

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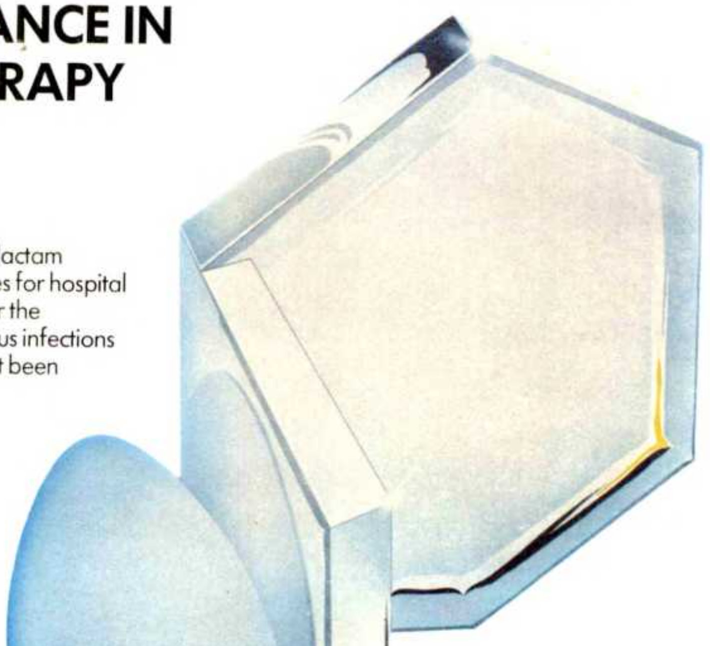

[cefuroxime] '...is highly resistant to degradation by ß-lactamases.'
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With important therapeutic properties

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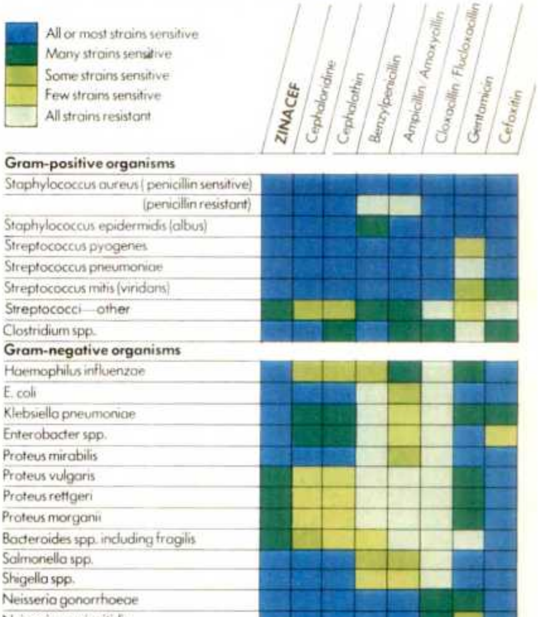

🟦 All or most strains sensitive
🟩 Many strains sensitive
▨ Some strains sensitive
🟨 Few strains sensitive
⬜ All strains resistant

	ZINACEF	Cephaloridine	Cephalothin	Benzylpenicillin	Ampicillin/Amoxycillin	Cloxacillin/Flucloxacillin	Gentamicin	Cefoxitin
Gram-positive organisms								
Staphylococcus aureus (penicillin sensitive)	🟦	🟦	🟦	🟦	🟦	🟦	🟦	🟦
(penicillin resistant)	🟦	🟦	🟦	⬜	⬜	🟦	🟦	🟦
Staphylococcus epidermidis (albus)	🟦	🟦	🟦	🟩	🟦	🟦	🟦	🟦
Streptococcus pyogenes	🟦	🟦	🟦	🟦	🟦	🟦	▨	🟦
Streptococcus pneumoniae	🟦	🟦	🟦	🟦	🟦	🟦	⬜	🟦
Streptococcus mitis (viridans)	🟦	🟦	🟦	🟦	🟦	🟦	▨	🟩
Streptococci—other	🟩	▨	▨	🟩	🟩	⬜	▨	⬜
Clostridium spp.	🟦	🟦	🟩	🟦	🟩	🟩	⬜	🟩
Gram-negative organisms								
Haemophilus influenzae	🟦	▨	▨	▨	🟩	⬜	🟩	🟦
E. coli	🟦	🟦	🟦	⬜	▨	⬜	🟦	🟦
Klebsiella pneumoniae	🟦	🟩	🟩	⬜	🟨	⬜	🟩	🟩
Enterobacter spp.	🟦	🟩	🟩	⬜	🟨	⬜	🟦	🟨
Proteus mirabilis	🟦	🟦	🟦	⬜	▨	⬜	🟦	🟦
Proteus vulgaris	🟩	🟨	🟨	⬜	⬜	⬜	🟩	🟦
Proteus rettgeri	🟩	🟨	🟨	⬜	⬜	⬜	🟩	🟦
Proteus morganii	🟩	🟨	🟨	⬜	⬜	⬜	🟩	🟦
Bacteroides spp. including fragilis	🟩	▨	🟨	🟨	⬜	⬜	⬜	🟦
Salmonella spp.	🟦	🟦	🟦	▨	▨	⬜	🟦	🟦
Shigella spp.	🟦	🟦	🟦	🟨	🟨	⬜	🟦	🟦
Neisseria gonorrhoeae	🟦	🟦	🟦	🟦	🟦	🟩	🟩	🟦
Neisseria meningitidis	🟦	🟦	🟦	🟦	🟦	🟩	🟨	🟦
Pseudomonas aeruginosa	⬜	⬜	⬜	⬜	⬜	⬜	🟩	⬜

ZINACEF

Prescribing information

Presentation
Vials of 250mg, 750mg and 1·5 gram and infusion pack of 1·5 gram. All containing cefuroxime as cefuroxime sodium.

Indications
Serious bacterial infection, especially where the organisms have not yet been identified.
Conditions include:
Chest infections
Septicaemia
Soft tissue infections
Obstetric and gynaecological infections
Bone and joint infections
Urinary tract infections
Ear, nose and throat infections
Meningitis
Gonorrhoea

Dosage
Adults: Generally 750mg t.d.s. i.m. or i.v. Severe infections 1·5 gram t.d.s. i.v. Frequency of injections can be increased to six-hourly if necessary.
Infants and children: 30 to 100mg/kg/day in three or four divided doses. 60mg/kg/day will be appropriate for most infections.
Neonates: 30 to 100mg/kg/day in two or three divided doses.
Gonorrhoea: Single dose of 1·5 gram (2 x 750mg i.m. into different sites).

Contra-indications
Hypersensitivity to cephalosporins.

Precautions
Cephalosporins may, in general, be given safely to patients who are hypersensitive to penicillins.
As with all drugs, Zinacef should be administered with caution during the early months of pregnancy.
Zinacef does not interfere with enzyme-based tests for glycosuria.
Cephalosporins interfere with tests for glycosuria which use copper reduction or ferricyanide methods and with the alkaline picrate assay for creatinine.
As with other antibiotics, prolonged use may result in the overgrowth of non-susceptible organisms.
Zinacef should not be mixed in the syringe with aminoglycoside antibiotics.
Reduce dosage when renal function is markedly impaired.

Cephalosporins at high dosage should be given with caution to patients receiving concurrent treatment with potent diuretics such as frusemide, as these combinations are suspected of adversely affecting renal function. Clinical experience with Zinacef has shown that this is not likely to be a problem at the recommended dose levels.

Side effects
Adverse reactions are rare and generally mild and transient, e.g., rashes, gastro-intestinal disturbance, candida intertrigo, decreased haemoglobin concentration, eosinophilia, a positive Coombs' test, transient rises in serum liver enzymes and transient pain (after i.m. injection).

Storage
The powder in the infusion pack and vials should be stored below 25°C and protected from light.

Product Licence number
4/0263

Price to Hospital (exclusive of VAT)

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5 x 750mg	2·10 per vial
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Br. J. Dis. Chest (1979) *73*, 81

FENOTEROL IN ASTHMA

G. ANDERSON, E. WILKINS AND A. G. JARIWALLA

St Woolos Hospital, Newport, Gwent

Summary

Fenoterol is a β_2-sympathomimetic bronchodilator. In a double-blind cross-over trial in 17 asthmatic patients with reversible airway obstruction inhalation of both fenoterol (0.4 mg) and terbutaline (0.5 mg) produced a statistically significant greater increase in peak expiratory flow rate than did placebo. The magnitude and duration of response to fenoterol exceeded that to terbutaline in the doses used. The patients' subjective assessment also suggested the relief of their symptoms with the active drugs. Side effects were minimal.

INTRODUCTION

Fenoterol (hydroxyphenylorciprenaline) is a sympathomimetic agent with a high affinity for the β_2-adrenergic receptors in the bronchial musculature. This study compares the magnitude and duration of action of inhaled placebo, terbutaline and fenoterol in patients with bronchial asthma.

Patients and Methods

Seventeen patients with bronchial asthma were studied. All showed an improvement in peak expiratory flow rate (PEFR) exceeding 20% 5 min after inhaling 2 puffs (0.16 mg) of isoprenaline. The characteristics of the patients are shown in Table I. All bronchodilator drugs were discontinued at least 10 hours before the trial and during the whole of the trial period but patients taking corticosteroids and sodium cromoglycate continued to do so.

Table I. Details of 17 patients studied

Males	11
Age (years, mean and range)	52 (22–70)
Positive skin tests	9
Blood eosinophilia ($>0.5\times10^9$/litre)	5
Steroid treatment during trial	9
Cromoglycate treatment during trial	10

After giving informed consent, patients were trained to record PEFR following the method of Lal et al. (1974). On a practice day before the trial they were instructed on rising to make three readings of PEFR at 10-min intervals until two consecutive readings were within 10 litres/min. The higher reading was accepted as a basal value (time 0). Three PEFRs were recorded after 10, 20, 30 min and 1, 2, 3, 4, 6, 8 and 10 hours after the basal value. Values were recorded on a standard form on which patients were specifically requested to record any side effects and the time of their occurrence.

Patients recorded a subjective impression of their breathing during the test day. This was compared to that on the day before the trial and scored as 1, worse; 2, no change; 3, a little better; 4, much better; 5, very much better.

After completing the practice day patients were studied over three consecutive days and were given three sealed envelopes each containing an indistinguishable inhaler. Each patient received in random order on three consecutive days 2 puffs of each inhaler giving fenoterol 0.4 mg, terbutaline 0.5 mg and placebo. The inhalers were given between 8.00 and 9.00 hours immediately after obtaining basal values for PEFR. PEFR recordings were made at the same intervals as on the practice day and similar recordings were made of side effects and breathing scores.

RESULTS

Fig. 1 shows mean values of PEFR (± SE). There were no significant differences between the initial PEFR on the three treatment days. The PEFR values were significantly higher at all time points on the fenoterol day compared with both the placebo day ($P < 0.01$, Duncan's multiple range test) and the terbutaline day ($P < 0.05$). The PEFR readings on the terbutaline day were significantly higher than those on the placebo day for 4 hours after inhalation ($P < 0.05$) but not subsequently. Comparison of initial PEFR values with those at 1 and 10 hours on each treatment day demonstrated highly significant differences from the initial at 1 and 10 hours on the fenoterol day ($P < 0{\cdot}001$,

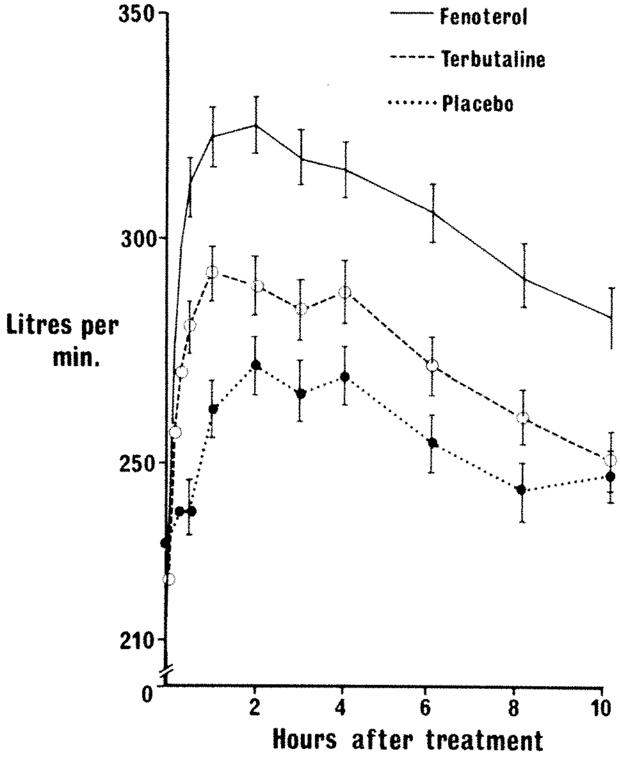

Fig. 1. Peak expiratory flow rate (mean ± SE) after inhalation of 0.4 mg fenoterol, 0.5 mg terbutaline or placebo

Table II. Results of breathing scores

Result	*Fenoterol*	*Terbutaline*	*Placebo*
Worse	0	1	7
No change	3	7	5
A little better	5	6	3
Much better	7	2	1
Very much better	2	1	1

paired *t*-test) and on the terbutaline day ($P < 0.001$) but at only 1 hour on the placebo day ($P < 0.01$).

The breathing scores are shown in Table II. Breathing scores were significantly higher on the fenoterol than on the placebo day ($P < 0.01$, distribution free multiple comparison) but although scores were higher on fenoterol than on terbutaline, and greater on terbutaline than placebo, these differences did not reach statistical significance.

The incidence of side effects (Table III) was similar on all 3 days and none was severe.

Table III. Side-effects in 17 patients

Side effect	*Fenoterol*	*Terbutaline*	*Placebo*
Light headed	2	2	2
Chest pain	1	2	4
Husky voice	1	—	—
Coughing	1	—	—
Fainting and diarrhoea	—	1	—
Tremor	1	—	—
Difficulty focusing	1	—	—
Tinnitus	—	1	—

DISCUSSION

It has been suggested (Brittain et al. 1970) that an increasing size of nitrogen-attached moiety on a catechol or resorcinol base leads to increasing β_2-specificity. Fenoterol has an extremely large moiety attached to the terminal nitrogen and might be expected to be a highly selective β_2-stimulant. This is confirmed by pharmacological studies in animals (O'Donnell 1972) and clinical studies in man (Leblanc 1972). In aerosol form it was shown to have a bronchodilator effect throughout a 3-hour study (McLeod & Selman 1973). In the present trial inhaled terbutaline was used as a comparison because it has a prolonged action (Leifer & Wittig 1975) and both drugs were administered in doses recommended in the manufacturers' data sheets. In the doses used fenoterol was shown to possess a bronchodilator effect exceeding that of terbutaline in magnitude and duration with a significant effect at 10 hours. In bronchitic patients Manicatide et al (1973) found that doses of inhaled fenoterol and terbutaline identical to those in this study gave virtually the same improvements in 1 second forced expiratory volume 1 hour after inhalation but at 5 hours the improvement over basal values was 6% with terbutaline and 15% with fenoterol.

The breathing scores reflected the objective improvements in PEFR between placebo and fenoterol. Except for tremor noted by a single patient on fenoterol the side effects were of a non-specific nature and likely to be placebo effects. Thus, 4 patients developed chest pain on placebo treatment.

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Br. J. Dis. Chest (1979) *73*, 85

GRANULAR CELL TUMOUR OF TRACHEA: REPORT OF A CASE

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Summary

A case of granular cell tumour of the trachea found at autopsy in a patient with a ten-year history of dyspnoea and wheezing is presented, with a brief review of the literature.

INTRODUCTION

Granular cell tumours (myoblastomas) are histologically distinctive tumours occurring most commonly in the skin and the tongue. A granular cell tumour of the trachea was found at autopsy on a patient at the University of Benin Teaching Hospital, Nigeria, and appeared to be responsible for the death of the patient. In view of the unusual site and clinical manifestations of this tumour it appears worth reporting.

Case Report

A 35-year-old African woman was seen in the Casualty Department of the University of Benin Teaching Hospital suffering from severe dyspnoea and wheezing of sudden onset. She had had similar but milder episodes over the previous ten years, and had been treated as suffering from bronchial asthma. On this occasion, however, her symptoms were very severe and she died before any treatment could be started.

At autopsy the body was that of an obese African woman aged about 35 years. There was no jaundice, lymphadenopathy, digital clubbing or oedema.

The salient findings on examining the organs were as follows. (*a*) The presence of tiny superficial ulcers in the caecum. These did not have the gross or histological appearance of amoebic or tuberculous lesions, and their significance was not clear. (*b*) Extensive bilateral lower lobe pneumonia. (*c*) The presence of a tumour in the middle third of the trachea. The mass was about 2.5 cm in diameter and protruded into the lumen, causing almost total occlusion (Fig. 1). The luminal suface was rough, and the first impression was that of a papilloma. On sectioning, however, the cut surface was bright yellow and the lesion was seen to have extended through the wall of the trachea into the adjacent soft tissue.

The surface epithelium was respiratory in nature, and was pushed up by the tumour mass, and ulcerated in places. No epithelial hyperplasia was seen. The arrangement of tumour tissue varied between the superficial and deeper parts of the tumour. Just under the epithelium the tumour was made up of elongated cells arranged in diffuse sheets (Fig. 2). These cells had a small dark nucleus and abundant pale granular cytoplasm. The deeper parts of the tumour showed the typical picture of a granular cell tumour, with distinct small islands of large polyhedral cells with inconspicuous nuclei and a large amount of granular cytoplasm (Fig. 3). The granules in both superficial and deep cells were strongly PAS positive. Few mitotic figures were seen.

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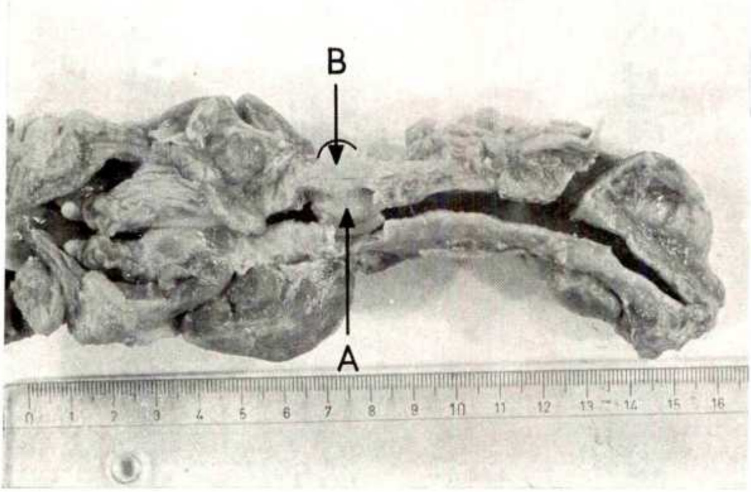

Fig. 1. Specimen of larynx and trachea, with the two major bronchi, showing tumour in the trachea. A, Tumour protruding into lumen. B, Tumour invading the wall

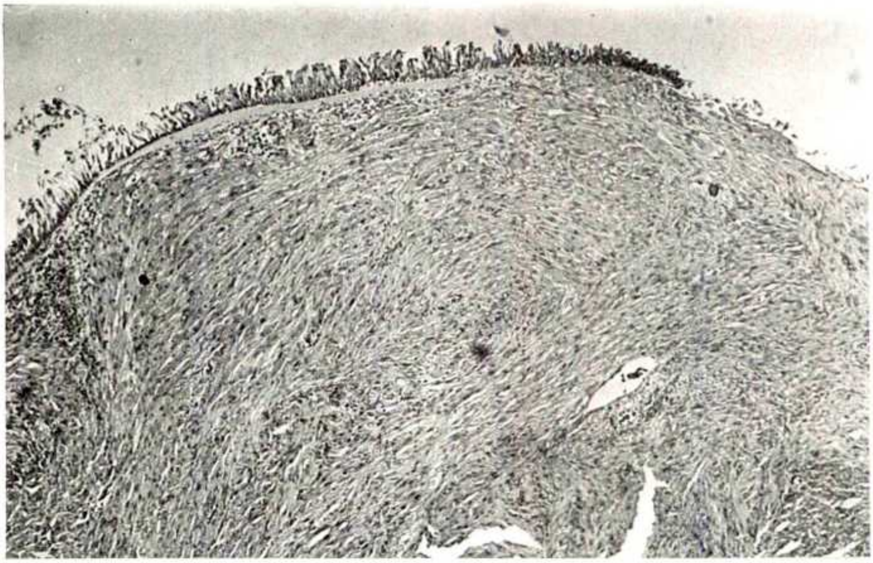

Fig. 2. Tumour mass composed of sheets of spindle cells with inconspicuous nuclei, covered by respiratory epithelium. H & E × 28

DISCUSSION

Granular cell tumours (myoblastomas) are defined as growths of mesenchymal origin, the cells of which are featured by the presence of granules that are sometimes acidophilic and stain positively with the periodic acid–Schiff stain. They were first described by

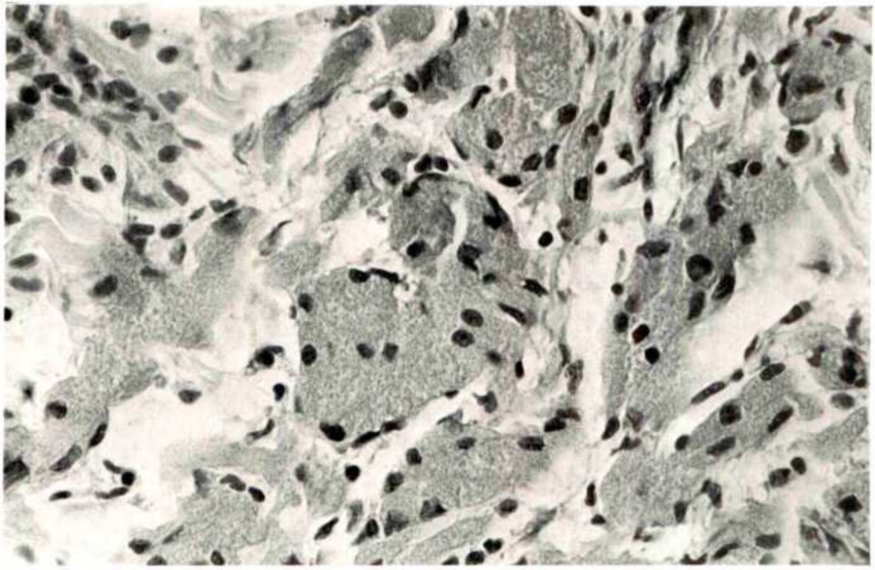

Fig. 3. Islands of large polyhedral cells, with inconspicuous nuclei and abundant granular cytoplasm. H & E ×280

Abrikossoff (1926), who considered them to be of skeletal muscle origin and used the term 'myoblastic myoma', altering it later to 'granular cell myoblastoma'. Other workers have suggested, on the basis of electron microscopic and histochemical characteristics, that they are related to Schwann cells (Fischer & Wechsler 1962); this has not been confirmed by tissue culture (Murray 1951). A possible origin from undifferentiated mesenchymal cells has also been suggested (Sobel & Marquet 1974).

The commonest sites of occurrence of these tumours are the tongue and the skin. Booth and Osborn (1970) found over 500 cases in the literature; 35% were from the tongue, 30% from the skin and nearly 20% from the respiratory tract. However these figures may not give a true picture as tumours occurring at unusual sites have a greater chance of being reported. Vance and Hudson (1969) analysed a collection of 50 such tumours and only three were in the respiratory tract. Strong et el. (1970) have obtained very similar results, with only four tumours in the respiratory tract out of a total of 110 tumours in 95 patients. Very few granular cell tumours have been reported in the trachea. Perelman and Korolewa (1973) analysed 73 tumours of the trachea; there was not a single case of granular cell tumour. Benson (1966) found 29 granular cell tumours of the lower respiratory tract in the literature and added 7; out of these 36 cases only three were in the trachea and five in the carinal region. Vance and Hudson (1969) found only one tumour out of 50 to lie in the trachea. Sargent et el. (1972) reported one case; they have stated that they found 49 previous cases in the literature. This would appear to be an exaggeration as some of the cases they have included are tumours of the larynx.

The majority of granular cell tumours appear to occur in patients between the ages of 30 and 50 years (Benson 1966; Vance & Hudson 1969). They are reported to be more frequent in females than in males, and in Negroes than Caucasians (Vance & Hudson 1969). Granular cell tumours do not, however, appear to be particularly common in

Africa. A review of over 600 soft tissue tumours in two centres in Nigeria has turned up only one more granular cell tumour. Out of 2840 soft tissue tumours seen in Uganda in a five-year period, there were only 16 granular cell tumours (Templeton 1973).

The majority of granular cell tumours are benign, though malignant varieties are known (Stout & Lattes 1967). The present case showed certain puzzling features in that the tumour had infiltrated and extended outside the wall of the trachea. However, there was little mitotic activity. If the patient's 10-year history of dyspnoeic episodes was entirely due to the tumour, this would imply that the lesion was of very slow growth, and should therefore be considered a benign growth with mild local infiltrative activity.

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OCCUPATIONAL ASTHMA STUDY BY INDUSTRIAL INJURIES ADVISORY COUNCIL

The Industrial Injuries Advisory Council has been asked by the Secretary of State for Social Services to consider whether occupationally induced asthma, caused by exposure to substances encountered at work, should be prescribed as an industrial disease.

A disease may be prescribed if it can properly be regarded as a risk of occupation and not a risk common to everyone, and if the occupational link can be established in particular cases or presumed with reasonable certainty. In the course of its study, the Council will be concerned to identify occupations, and substances used in those occupations, which may give rise to occupational asthma; and to consider the medical aspects, including the problem of distinguishing occupationally-caused asthma from non-occupationally caused asthma.

A number of substances which are commonly encountered at work are believed to be associated with asthma including isocyanates, penicillin, grain dust, flour, wood dusts and biological washing powders. Some of these substances are also widely met outside the working environment.

The Council wishes to receive evidence from any interested persons or organisations and will supply a short explanatory memorandum on request. Evidence and communications should be sent to the secretary, Industrial Injuries Advisory Council, Room 511 (A 20) Keysign House, 429 Oxford Street, London W1R 2HT as soon as possible and not later than 31 January 1979

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Short Communication

HYPONATRAEMIA AND MESOTHELIOMA

W. H. PERKS, R. STANHOPE AND M. GREEN

Brompton Hospital, London

Summary

Hyponatraemia was found in 18 (62%) of 29 patients with histologically proven mesothelioma. The mechanism for the development of the hyponatraemia is discussed. It is suggested that patients with mesothelioma should be monitored for electrolyte abnormalities. If hyponatraemia is found the syndrome of inappropriate secretion of antidiuretic hormone should be suspected as treatment with demethylchlortetracycline may improve the quality of life in an otherwise fatal illness.

INTRODUCTION

A patient with the syndrome of inappropriate secretion of antiduretic hormone (ADH) associated with a pleural mesothelioma has recently been described (Perks et al. 1978). It was postulated that the ADH hypersecretion was mediated through a vagal reflex, either from involvement of the pulmonary baroreceptors or by direct stimulation of vagal afferents by tumour. For this hypothesis to be correct the inappropriate ADH syndrome should be common in patients with pleural mesothelioma. Careful review of the mesothelioma literature, however, revealed no other reports of this association. To ascertain the frequency of hyponatraemia in patients with mesothelioma we performed a retrospective analysis of the records of patients admitted to Brompton Hospital.

Patients, Materials and Methods

The records of 37 patients with histologically proven mesothelioma admitted to Brompton Hospital were examined. The age at diagnosis, sex and the serum electrolytes (sodium potassium

Table I. Serum electrolytes of patients with mesothelioma, controls and normal values

	Mesothelioma	*Controls*	*Normal values*	*Significance*
Number	29	29	—	—
Lowest serum sodium (mmol/litre; mean ±SD)	133.8±5.4	139.4±1.6	135–145	$P<0.001$*
Number with lowest sodium less than 135 mmol/litre (% total)	18 (62)	0 (0)	—	$P<0.001$†
Number with lowest sodium less than 130 mmol/litre (% total)	7 (24)	0 (0)	—	$P<0.01$†
Serum urea (mmol/litre; mean)	4.5	5.0	2.5–5.8	Not significant*
Serum potassium (mmol/litre; mean ±SD)	4.2±0.4	4.1±0.4	3.8–4.8	Not significant*

* Mann–Whitney *U*-test.

† Fisher's exact probability test.

and urea) were recorded. Electrolyte measurements made during treatment with diuretics, corticosteroids or drugs known to produce hyponatremia were excluded. Similarly measurements within 14 days after surgical operation or within 28 days of death were excluded. This left 29 patients with mesothelioma and estimates of plasma electrolyte levels who fulfilled the criteria for analysis. In each patient the electrolyte studies with the lowest serum sodium were analysed. Control subjects with chronic bronchitis, asthma or bronchiectasis matched for age and sex were taken randomly from the in-patient medical records. The electrolytes with the lowest serum sodium were obtained as with the mesothelioma patients. The mean age of both groups was 53 years (standard deviation ±10) and the male/female ratio was 6.4:1. As the distribution of the data was not Gaussian, non-parametric statistical analysis was used. Hyponatraemia was significantly more common in the mesothelioma patients. There was no significant difference in serum levels of urea and potassium between the two groups (Table I).

Discussion

The inappropriate ADH syndrome can be diagnosed when there is hyponatraemia, a low serum osmolality and simultaneously a less than maximally dilute urine (De Troyer & Demanet 1976). Although hyponatraemia occurred in 62% of our patients with mesothelioma they had not been fully investigated with matched osmolalities because the inappropriate ADH syndrome was not suspected. However, the most likely cause of the hyponatraemia is inappropriate secretion of ADH since other causes were excluded by our selection of patients and the absence of abnormalities in serum levels of urea and potassium.

Ectopic production of hormones has not been described with mesothelioma and is rare in other tumours of mesenchymal origin. Hypoglycaemia and hypophosphataemic osteomalacia are occasionally found with mesenchymal tumours, although there is uncertainty whether there is an ectopic humoral syndrome in the latter case (Rees 1975). It seems unlikely therefore that the hyponatraemia in our patients was caused by the ectopic production of ADH by the tumour. Perks et al. (1978) have recently proposed secretion of ADH as a reflex via the vagus nerve to be the mechanism for the hyponatraemia associated with mesothelioma. The pulmonary baroreceptors acting via the vagus are important in controlling the release of ADH from the posterior pituitary; for example loss of intravascular volume or positive pressure ventilation leads to secretion of ADH (Kleeman 1970). Compression of the pulmonary baroreceptors or infiltration of the vagus nerve by mesothelial tumour could therefore lead to reflex secretion of ADH. Against this hypothesis is the absence of previous reports of the association of hyponatraemia with mesothelioma. The finding of hyponatraemia commonly in patients with mesothelioma is further evidence for a reflex mechanism for the secretion of ADH with mesothelioma.

Finally, all patients with mesothelial tumours should be investigated for the inappropriate ADH syndrome since treatment with demethylchlortetracycline may improve the quality of life in an otherwise fatal condition (Perks et al. 1976).

Acknowledgements

We thank Mrs Ellen Dyche for secretarial help and Mr D. Brown for statistical advice.

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BOOK REVIEWS

Preventing Bronchitis

London: Office of Health Economics. 1977. Pp. 40. Price 35p

This is a mine of up-to-date information and it should certainly be read by all chest physicians and those practising preventive medicine. Before 1950 very few papers were published on chronic bronchitis. The great smog of 1952 stimulated public concern and led to the Clean Air Act of 1956. The many papers published in the last 10 years have been carefully, critically summarized and should be particularly helpful to students undertaking projects on this subject.

A few of the many facts produced are as follows:

Chronic bronchitis costs the National Health Service £100 million a year.

Community burden amounts to £250 million pounds a year in loss of production.

Between 1952 and 1965 smoke emission in the UK fell by 84%.

In non-smokers the effects of atmospheric pollution are relatively mild, but in established smokers its adverse influence becomes increasingly marked with rise in cigarette consumption.

Chronic bronchitis still affects the British population to a greater extent than that of any other country.

Health education is least effective amongst the lower social classes who already incur a seven times greater risk of dying from bronchitis than the more affluent classes.

Fortunately there has been a considerable reduction in the distress caused by chronic bronchitis in recent decades and the standardized mortality rates have fallen for both men and women. But while occupational and environmental pollution has declined, cigarette smoking has increased. Britain as yet has no long-term publicly announced tax strategy for control of the cigarette habit. Bringing British taxes into line with those of the EEC may actually encourage 'king size' cigarettes. We cannot be satisfied while there are still over a million people in Britain suffering from chronic bronchitis, as shown by persistent sputum production and acute exacerbations with shortness of breath. With further improvements in clean air and continued fall in cigarette sales, we may hope that chronic bronchitis will follow cholera, dysentery and malnutrition as conditions mainly of historical importance. The recommendations in this booklet should encourage this process.

KEITH P. BALL

The British Thoracic Association: The First Fifty Years

London: British Thoracic Association. 1978. Pp. x + 126. Price £4.50

The British Thoracic Association began its life half a century ago in the joining together of the Tuberculosis Society founded in 1911 and the Society of Superintendents of Tuberculosis Institutions founded in 1920. The union was a somewhat reluctant one; as a physician recorded at the time, 'we looked at each other as members of a different race of beings', but the union came about, despite internal opposition, because of the pressing need to tackle the seemingly insoluble problem of tuberculosis in the United Kingdom. So the two societies became the Tuberculosis Association.

Twenty years later, in 1948, with its membership and influence increasing, and to emphasize its national role, it added 'British' to its name, and became known the world over as the BTA. In 1966 the Joint Tuberculosis Council gave up independent status and joined the BTA, and this further increased its prestige and usefulness. By now the diminishing problem of tuberculosis and the rapidly expanding interest in other aspects of thoracic medicine led to a call for a change of name. 'British Thoracic Association' was resisted; in the view of many it was too soon to drop 'Tuberculosis' from the title. Also resisted, but reluctantly because its abbreviation was so easy to remember, was the suggestion, 'British Association for the Study of Tuberculosis And Respiratory Diseases'. In 1968 a compromise was reached and it became the British Thoracic and Tuberculosis Association. Then, in 1977, without much opposition came the latest alteration, the British Thoracic Association, and so from BTA to BTA in one generation.

This small book, written to mark the fiftieth anniversary of the Association, is a most readable account of its history. The story is vividly told of the times and of the men who played such an important role in moulding thoracic services in this country as we know them today.

Those concerned with the writing of this book deserve praise. It is a fascinating story that many thoracic physicians will want to read.

MAXWELL CAPLIN

Lung Biology in Health and Disease, 4. Metabolic Functions of the Lung

Y. S. Bakhle and J. R. Vane

New York: Marcel Dekker. 1977. Pp. xvi + 353. Price SFr 112

Lung Biology in Health and Disease, 6. Development of the Lungs

W. Alan Hodson

New York: Marcel Dekker. 1977. Pp. xxii + 646. Price SFr 160

Of Advances and Recent Trends, of Modern Concepts and Workshops, of Year Books and Annual Reviews and Current Topics, indeed All Sorts of Series of Medical Books there appears to be no end, and here is another one. This one is several cuts above the average, probably at least three standard deviations.

The idea of the lung as a metabolic organ has now been circulating long enough to deserve an efficient capillary filter in the form of a monograph. There is about 15 years work to review, the authors appear to be actively in the business as opposed to being in retirement but still drawing director's fees, and the resulting book (Volume 4) is a success. It will not change the reader's clinical practice overnight, nor will present knowledge explain much clinical pathophysiology—yet. There are major measurement problems, and the inability for example easily to separate and quantify bronchodilator and bronchoconstrictor prostaglandins in small quantities of blood means that a hypothesis incorporating suitable quantities of both can be constructed to account for almost any clinical observation. (This temptation is eschewed, mostly, by the authors.) Nevertheless, it is an important field and a reader wishing an introduction to it or a summary of it could do no better than to start here.

The problems of pulmonary function and respiratory control in premature infants, especially hyaline membrane disease, and the dramatic pathology of congenital heart disease, ensured the early attention of some of the most talented post-war scientists, many of whom have contributed to Volume 6 on the Development of the Lung. This applies not only to airways, alveoli and blood vessels but also to surface-active material, innervation of the lung, respiratory control, and the physiology of gas exchange, mechanics and control of the pulmonary circulation. The result is an authoritative, critical and comprehensive account.

Dr Lenfant (General Editor) is to be congratulated on attracting authors of such high calibre to contribute to these two volumes, and in ensuring an even clear style. The books are well produced, with references up to 1976 or 1977, and can be confidently recommended.

K. B. SAUNDERS

Current Therapy 1977

Howard F. Conn

Philadelphia and London: W. B. Saunders. 1977. Pp. xlii + 689. Price £19.50

This book contains 284 articles written by 343 contributors. It sets out to describe, 'latest approved methods of treatment' for a wide range of diseases from acanthocytosis to Zenker's diverticula, but it does not say who does the approving. The treatment described in each case is the 'method' of the individual contributor, and references are omitted entirely. Such descriptions may be biased and disputable; they are of no use to the specialist and can be misleading to doctors working in other fields. The book costs almost £20; its size and weight (5 lb) preclude its use as a handy guide to therapy for the junior doctor and I can see no place for it in any situation where developed medical services are available.

B. S. MANTELL

Clinical Physiology of the Lung

Kenneth B. Saunders

Oxford: Blackwell Scientific. 1977. Pp. vi+255. Price £9.75

This is an interesting and ambitious book in which the author seeks to bridge the gap between the many books which deal with the fundamentals of respiratory physiology and medicine, on the one hand, and the more comprehensive textbooks and detailed reviews on the other. It is aimed at those who wish to become 'professionals in chest medicine'. There are seven chapters, four mainly physiological and three clinical, and in each of these Dr Saunders, assuming some basic knowledge—at about the undergraduate level—moves fairly rapidly through important established principles and concepts on to advanced topics and their advancing fringes. His approach is refreshingly individualistic, both in terms of selection of topics and in the way he deals with them, which is predominantly mathematical and numerical rather than trying to induce an intuitive understanding. The result, perhaps inevitably, is a rather uneven standard between chapters.

The first chapter, on Lung Mechanics, is comprehensive, with adequate emphasis being placed on the importance of surface forces and clear descriptions of recently developed (or revived) techniques of investigating 'small airways' function. However, the aspiring professional might find the run-up to the body plethysmograph a little too steep, and I am sure that some confusion might well arise between oesophageal balloon and plethysmographic methods of measuring resistance.

The chapter on Gas Exchange is similarly comprehensive and is sensibly based on the O_2–CO_2 diagram. However, the recent work of West and others on spread of $\dot{V}/\dot{Q}$ ratios is curiously not mentioned. This is followed by a short and rather didactic chapter on Acid–Base Balance, including clinical applications, to which I could take no exception apart from the author's loaded arguments in favour of pH rather than H^+ nomenclature.

For me, the best part of the book was the chapter on the Respiratory Control System in which Dr Saunders' expertise made for exciting reading. I learned a lot from this chapter and I am sure that hardened professionals would also enjoy it.

The three clinically orientated chapters on Asthma, Chronic Bronchitis and Emphysema, and Respiratory Failure are less detailed and largely unexceptionable. The author asks one or two challenging questions about our accepted views of respiratory failure.

The layout and presentation are good, as are the diagrams on the whole—but when will some enterprising medical publisher arrange diagrams and the relevant explanatory text on facing pages so that the reader does not have to be continually turning pages back and forth while trying to follow a difficult argument?

Dr Saunders' style is breezy and so, unfortunately, is the spelling, especially of names. I kept being annoyed by odd loose ends. For example, Rohrer's name is introduced into the text without any explanation of who he was or when he worked, nor with any reference to him at the end of the chapter.

Overall verdict—a very good book, but with more attention to detail it could have been excellent.

S. FREEDMAN

The Mediastinum: Radiological Correlations with Anatomy and Pathology

E. Robert Heitzman

St Louis: C. V. Mosby. 1977. Pp. xiv+341. Price $37.50

The mediastinum, because of its apparent uniform density on the plain film, has long been an area which has tended to be approached superficially and discussed rapidly by many clinicians. Using the same approach as in his earlier and companion volume, *The Lung: Radiological–Pathological Correlations*, Professor Heitzman emphasizes how an anatomical approach to radiological interpretation can yield information previously unsuspected.

The shortcomings of the standard classification of the mediastinum into superior, anterior, middle and posterior compartments is indicated if only for its superficial anatomical applications. An alternative scheme is presented, not as a standard classification, but rather as a 'rational approach to an understanding of anatomic relationships and their radiological significance'. Following a brief chapter on the preparation of body sections and a more lengthy chapter on more general radiological considerations, the remaining chapters each discuss an area or region described in the classification mentioned above.

Radiological techniques in general are but briefly discussed though greater space is given to the more recently developed procedure of computerized tomography. A number of very clear illustrations convincingly indicate the value of this latter technique both for definitive demonstration of mediastinal lesions and for the staging of neoplastic disease. The indications as seen at present for the use of computerized tomography are clearly set out. The anatomy of lymphatic pathways is also outlined and its use in assessing treatment and prognosis indicated.

In the subsequent chapters relating to the various areas of the mediastinum, the normal anatomy is first described and correlated in a clear and concise manner with the appropriate plain radiographs or tomographs. Where indicated the conclusions drawn are often confirmed by contrast studies of both patients and cadaver specimens. Pathological conditions are then considered in the same manner. Whilst the abnormal conditions described are not exhaustive, the commoner lesions are well covered.

The reader may not be immediately familiar with two of the regions which are considered in detail. These are the infra- and supra-azygos areas. Both of these require considerable knowledge of various 'mediastinal lines', for appreciation of both the normal and the abnormal. The author stresses that recognition of these lines is the basis of his correlations between radiology, anatomy and pathology. Whilst this is apparent in all sections, nowhere is it more so than in these two chapters.

The text is lucid. The quality of the illustrations is excellent and they have the added advantage that they are largely self-explanatory. Perhaps the captions might be more easily read and followed if they were beneath each print rather than in one block presentation. This is, however, a minor criticism.

This book can be enthusiastically recommended to all radiologists, chest physicians and pathologists who wish to further their understanding of mediastinal anatomy—normal and abnormal.

MICHAEL C. PEARSON

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THE BRITISH THORACIC ASSOCIATION

FUTURE MEETINGS OF THE BTA

2–5 July 1979	Churchill College, Cambridge. Jointly with the Swedish Thoracic Society
7 December 1979 (whole day)	Royal College of Physicians, London
9–11 April 1980	University of Swansea
Autumn 1980 (date to be finalized)	Norway. Jointly with the Norwegian Thoracic Society
5 December 1980	Royal College of Physicians, London. To be confirmed
Spring 1981	To be arranged
29 June–2 July 1981	The BTA and the Chest, Heart and Stroke Association have offered to host the European region of the International Union Against Tuberculosis at Churchill College, Cambridge
30 June–3 July 1982	University of York

Further details about these meetings may be obtained from Dr J. R. Mikhail, Royal National Hospital, Bourne Avenue, Bournemouth.

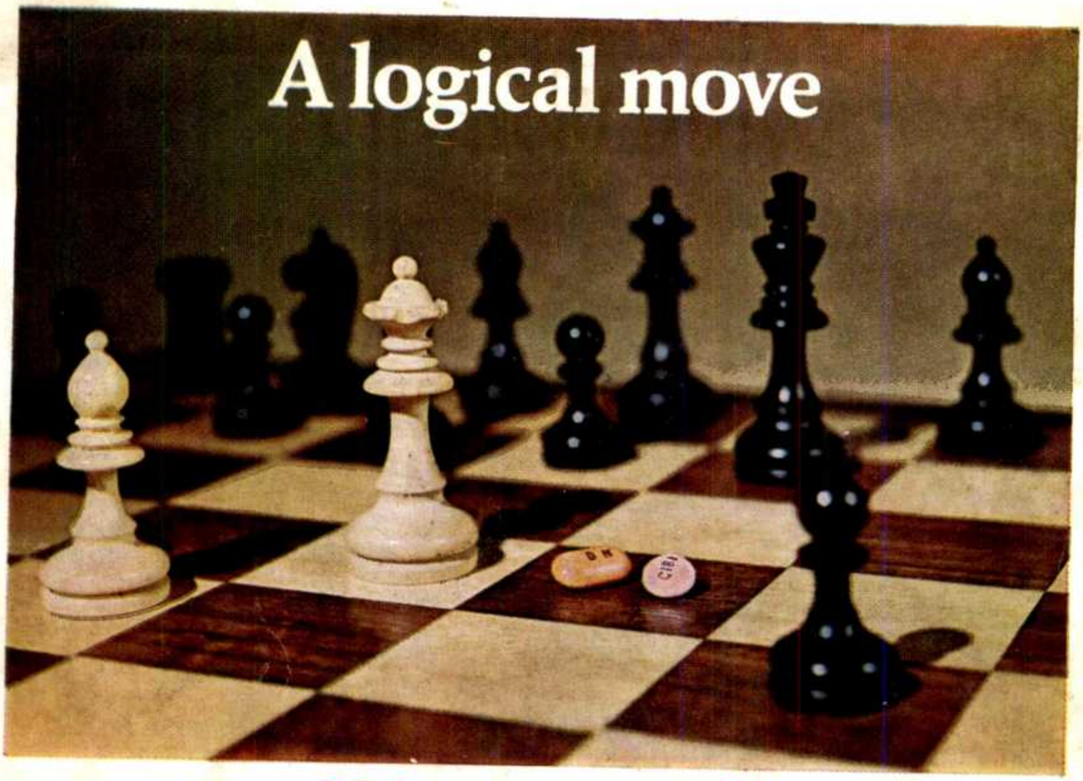
FUTURE MEETINGS OF THE THORACIC SOCIETY

1–3 February 1979	Royal College of Physicians, London. Members of the American Thoracic Society have been invited to attend
6–7 June 1979	Paris. Jointly with the French Thoracic Society
7–9 February 1980 (to be confirmed)	Royal College of Physicians, London
3–4 July 1980	Durham. Members of the BTA and the Belgian Thoracic Society are particularly invited to attend this meeting; details will be circulated

Further details about these meetings may be obtained from Dr S. W. Clarke, Department of Thoracic Medicine, Royal Free Hospital, Pond Street, London NW3 2QG.

PAPERS INVITED

The British Thoracic Association invites papers for presentation at its Annual Meeting for 1979, to be held in July 1979 at Churchill College, Cambridge, jointly with the Swedish Thoracic Society. Summaries of 200–300 words should be submitted to the Honorary Secretary, Dr J. R. Mikhail, Royal National Hospital, Bourne Avenue, Bournemouth, by 31 January 1979.



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METHODS OF STUDYING LOBAR AND SEGMENTAL FUNCTION OF THE LUNG IN MAN

S. J. Williams, R. J. Pierce, N. J. H. Davies and D. M. Denison

Brompton Hospital, London

Summary

Making the decision whether a patient with chest disease can undergo lung surgery may be easier if the anatomical extent of the disease and the functional effects of resection can be estimated. Although information can be gained by non-invasive physiological studies of lung function of a routine kind, these cannot define the anatomical extent of the disease or distinguish the relative influence of affected and unaffected parts as estimates of lung function. Whole lung ventilation and perfusion scans provide immediate topographic information but have limited resolution and anatomical accuracy, particularly when the architecture of the lung is disturbed by disease. Bronchoscopy gives direct visual information about the more central airways but little or none about the function of the areas they serve.

This paper gives brief descriptions of a series of procedures which could help in assessing the feasibility of lung surgery. The size, shape and volumes of individual lungs and lobes can be estimated from plain chest radiographs. Corresponding information about individual segments, and about lobes not delineated by normal X-ray, can be obtained using radio-active krypton 81m and a gamma camera during otherwise routine fibreoptic bronchosopy. Similarly the volume, alveolar ventilation and effective blood flow of lobes and segments can be determined by simple single-breath manoeuvres at bronchoscopy using a respiratory mass spectrometer. The radio-isotope and spectrometric tests can be obtained in the same breath. The spectrometric tests can be recorded from more than one part of the lung within the same breath. All of the procedures give information in terms of anatomical units of interest to the surgeon.

INTRODUCTION

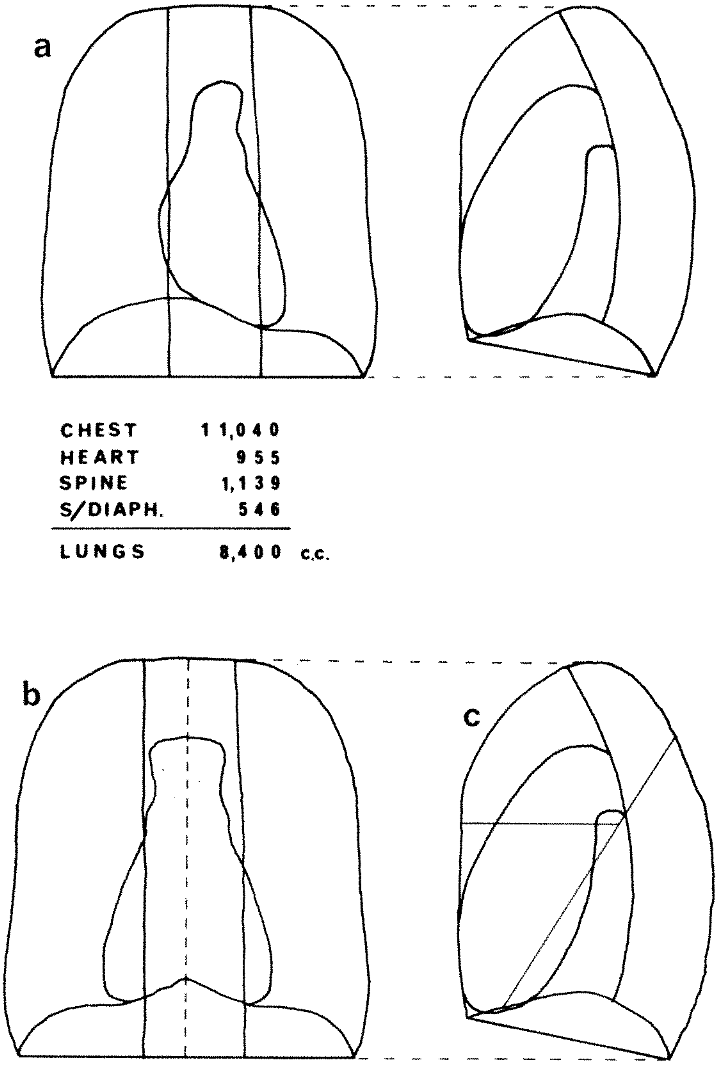
The severity of any functional disorder is unevenly spread through the lungs of patients with, for example, lung tumours, bronchiectasis, bullae and congenital cardiopulmonary disorders. Some of these patients are considered for surgery to remove the affected part of the lung. In them it is important to attempt to answer three questions:

1. What is the anatomical extent of the disease?
2. Is the affected part of the lung serving any useful function?
3. Is the remainder of the lung capable of supporting life if the affected part is removed?

In this paper we wish to give a brief account of tests we have developed to study the problems of answering these questions. The tests are simple to perform and provide estimations of static, dynamic and accessible gas volumes, alveolar ventilation and effective blood flow of any lobe or segment .

STATIC VOLUMES

Pierce et al. (1979) have shown, from anatomical and tomographic information, that the chest, heart, diaphragm and spinal mass are nearly elliptical in cross-section. This has enabled them to estimate the volumes of whole lungs from plain chest radiographs with



CHEST	11,040
HEART	955
SPINE	1,139
S/DIAPH.	546
LUNGS	8,400 c.c.

Fig. 1. Print-out obtained when calculating volume of (*a*) whole lung, (*b*) one lung and (*c*) lobes from a pair of plain radiographs

an accuracy of ±2.5% in normal subjects when compared with estimates from the body plethysmograph. Other workers have, of course, reported similar results from similar methods. Volumes are calculated from lateral and posteroanterior images of known magnification, using a manual digitizer, processor and display unit. If the boundaries of the individual lungs and lobes can be seen on the plain films their volumes can be measured in a similar manner (Pierce et al. 1979).

The principles involved are illustrated in Fig. 1. The volume of the whole lung is calculated by subtracting the volumes of the cardiac, subphrenic and spinal masses from that of the chest as a whole, assuming the chest cavity to be one-third of the way between an ellipse and its containing rectangle in cross-section, whereas the heart, diaphragm and spinal mass are strictly elliptical. For this purpose the phrenic boundary on the lateral film is drawn half-way between the two cupolae (Fig. 1*a*). To calculate the volume of an individual lung its posteroanterior view is, in effect, reflected about a mediastinal axis to give a symmetrical structure that can be treated as before, using the appropriate cupola as a boundary on the lateral film (Fig. 1*b*). Volumes of individual lobes are calculated supposing that the interlobar fissures appear in cross section as lines in the coronal plane (Fig. 1*c*). Using the equipment described, a complete set of lobar volumes can be obtained from a pair of films in a matter of minutes. Results calculated in this fashion from a normal subject are compared with anatomical and other data in Table I.

Table I. Volume of each lobe of a normal subject expressed as a percentage of whole lung measured by gas dilution at bronchoscopy and by the chest X-ray technique compared with anatomical data derived from Horsfield (1967)

	Bronchoscopic gas dilution (supine)	*Chest X-ray (erect)*	*Anatomical data*
Right upper lobe	13	16	20
Middle lobe	8	9	9
Right lower lobe	29	27	25
Left upper lobe including lingula	29	26	25
Left lower lobe	21	21	21

If the fissures of the lung cannot be seen clearly, or if segmental volumes are required, these parts of the lung can be outlined by radio-active gas and recorded with a gamma camera. Because of its short half-life (13 seconds) krypton 81m can be used to determine the size, shape and position of each segment or lobe of the lung in rapid succession during the course of a routine fibreoptic bronchoscopy. The krypton, which is generated by its parent isotope rubidium 81 (half-life 4.7 hours) can be eluted from the generator by a low flow (about 100 ml/minute) of any moist carrier gas (Fazio & Jones 1975). It is a simple matter to deflect the stream of gas so marked down the suction channel of the bronchoscope and direct it into any subdivision of the lung during a slow inspiration. In this manner we have obtained anterior and lateral views of all the lobes and segments of

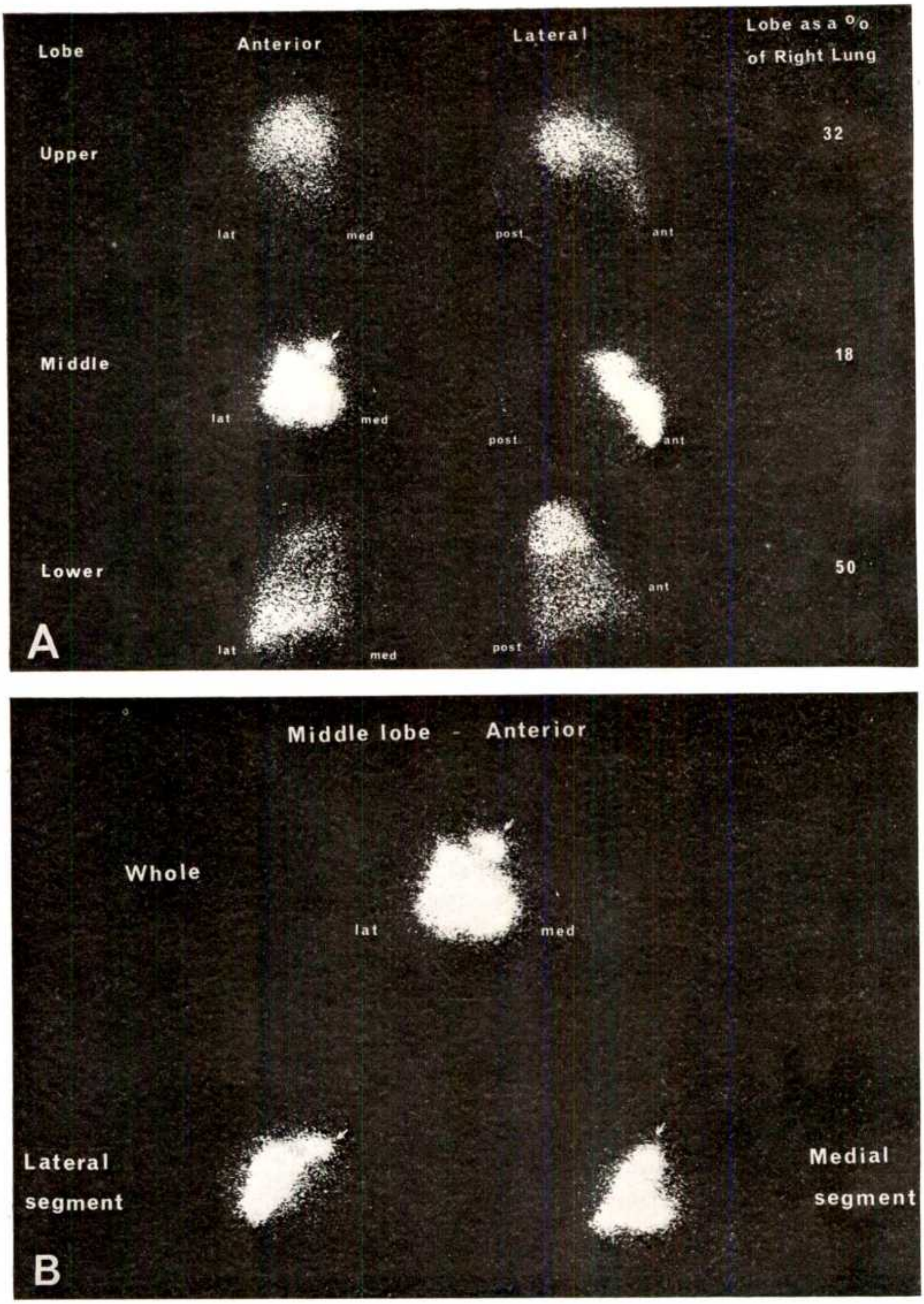


Fig. 2. A, Anterior and lateral krypton 81m scans of the lobes of the right lung in a normal supine subject. The volume of each lobe is expressed as a percentage of the right lung. B, Anterior krypton 81m scan of the middle lobe and its medial and lateral segments in a normal supine subject

the lung in normal subjects and patients with heart and chest disease. Examples from a normal subject are shown in Fig. 2. The displacement volumes of parts of the lung so outlined are calculated using the sample principles as for plain radiographs.

Often it is useful to display the positions of lobes and segments relative to known surface markings. The thin tube carrying the radio-active labelled gas from the generator to the bronchoscope can be used to outline the chest as in Fig. 3. In this case the tube has been taped to the lower rib, sternum, clavicle and anterior axillary line. Radiation to these structures is reduced by placing a flexible strip of lead (a draughtsman's curve) between them and the tube of gas.

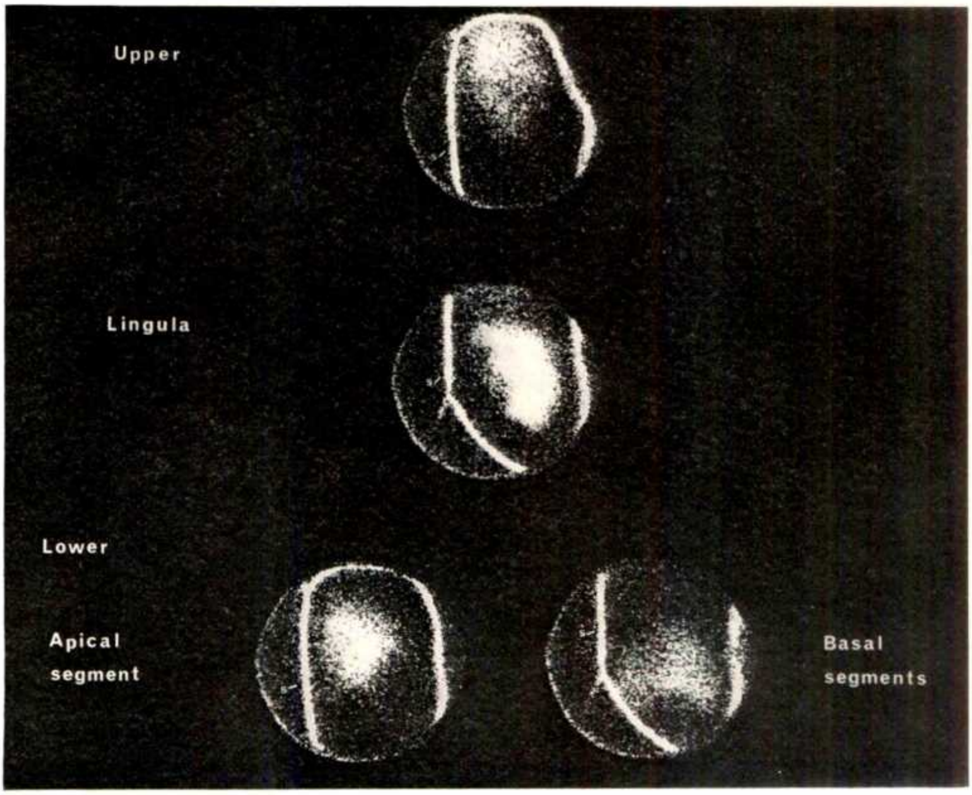


Fig. 3. Anterior krypton 81m scan of the lobes of the left lung in a normal supine subject. The lower costal margin, sternum, clavicle and anterior axillary line have been marked by a tube containing radioactive gas

It is also possible to instil marker into any airway during a breath-hold, outline the neighbouring parts of the bronchial tree, and observe how the marker is redistributed by phenomena such as cardiac beat mixing, convection, slow inspiration and pendular breathing. An example of this is shown in Fig. 4. Here the radio-active gas was instilled through the bronchoscope into the trachea of a normal, supine subject holding his breath at FRC. Pictures were taken at 1-second intervals using a Low Energy Mobile Camera (Searle) with a facility for rapid sequence imaging. The gas can be seen to be

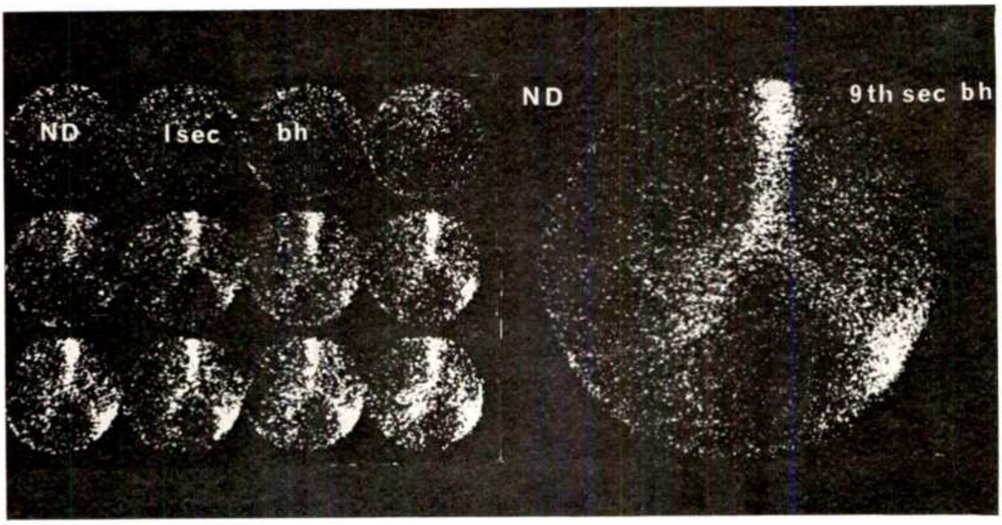


Fig. 4. Distribution of krypton 81m when instilled into the trachea of a normal subject breath-holding at FRC: pictures taken at 1-second intervals and after 9 seconds of breath-holding

carried into the left lung by cardiac beat mixing during the breath-hold at a time when little or none has reached the right lung. An enlarged view of the distribution of gas at the end of the ninth second of breath-holding is shown on the right of the figure.

DYNAMIC LUNG VOLUMES

Dynamic volumes of the whole lung are normally measured by conventional spirometry at the mouth. Until recently corresponding measurements on parts of the lung have been limited to observations on patients sedated sufficiently to accept quite large endobronchial tubes. The narrow fibreoptic bronchoscope is easily introduced into fully conscious patients who can cooperate in simple breathing procedures and is readily manoeuvred over a wide range of the bronchial tree. It is quite practical to pass a balloon catheter (e.g. a Swann-Ganz 4F) through the suction channel of the bronchoscope and inflate it to occlude part of the lung so that the spirometric behaviour of the remainder and the trapped part can be studied separately at the mouth.

Fig. 5 illustrates the information obtained over the course of three forced flow-volume loop manoeuvres from a 22-year-old man with severe stenosis of his left main bronchus. All records were taken with the tip of the bronchoscope lying in the trachea; in the first the balloon catheter was deflated, in the second it occluded the stenosed left main bronchus and in the third it occluded the relatively normal main bronchus on the right. The flow-volume loop obtained from the right lung, i.e. with the left main bronchus occluded, is normal though marred by two cough artefacts. Note that expiration is complete in less than three seconds. The loop recorded from the stenosed main bronchus on the left shows severe, pressure-dependant airway collapse, that is a marked reduction in forced expiratory flow rate at the onset of expiration. This lung empties more slowly than the right in that after three seconds a little under half of its vital capacity remains to be

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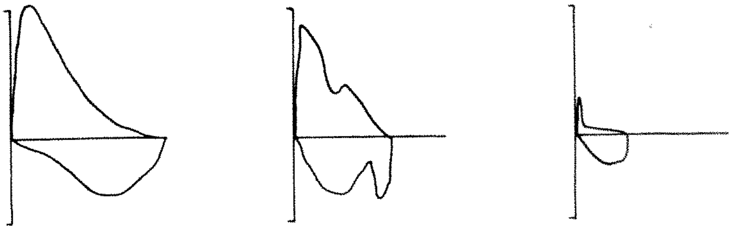


	Both lungs	**Right lung**	**Left lung**
PEF	6·31	5·25	1·95
FEV$_1$	2·59	2·18	0·28
FEV$_3$	3·37	2·48	0·70
FVC	3·72	2·48	1·32
FEV$_1$/FVC	69%	87%	21%

Fig. 5. Flow volume loops recorded at the mouth in a supine subject with severe stenosis of the left main bronchus

expired. The loop recorded from both lungs together can now be interpreted as a synthesis of one lung emptying and filling rapidly and a rather smaller lung emptying and filling more slowly

RESPIRATORY MASS SPECTROMETRY*

Respiratory mass spectrometry is a technique of rapid gas analysis which has been used extensively as a research tool since its development some 20 years ago (Fowler & Hugh-Jones 1957). Clinical versions of these analysers sample gas through flexible probes about 1 mm in diameter and up to 30 m long, at flows as low as 10–50 ml/minute. The analyser continuously determines the partial pressures of up to eight component gases of the sampled mixture simultaneously, with an accuracy of about ±1 mmHg and a 90% response time of around 0.1 second. The constituent gases to be studied can be chosen and varied at will. A minute fraction of the sample diffuses into the analyser at a very low pressure (10^{-7} mmHg) where it is ionized by a beam of electrons. The ions that are produced in this way are thrown in an electromagnetic field so that they fall on a detector

* Estimates of accessible gas volume, alveolar ventilation and effective blood flow about to be described have been made during otherwise routine fibreoptic bronchoscopies using a mass spectrometer.

plate in groups of similar mass (strictly mass/charge ratio). When the whole collecting field is scanned a spectrum is obtained of concentration (peak height) against mass charge ratio (peak position) and, effectively, this spectrum can be read at many points simultaneously. A sensitivity control circuit automatically compensates for any variations in the flow of gas reaching the machine.

Because the spectrometer has a small flexible probe and low sample flow it is easily adapted to endobronchial use. This was first shown by Hugh-Jones and West (1960) during rigid bronchoscopies on patients who were quite heavily sedated. The fibreoptic bronchoscope is more manoeuvrable and easily introduced into fully conscious patients under local anaesthesia. Thus it can be used to position the tip of the spectrometer probe at accurately known sites over a wide range of the bronchial tree. We use an Olympus BF-B3 bronchoscope and a Centronics 200 MGA spectrometer. The bronchoscope is passed through the nose in the usual way with the patient lying or sitting as required. Once any excess fluid or mucus has been removed from the bronchial tree the spectrometer probe is passed down the suction channel of the bronchoscope until it comes into view when it can be directed into the lumen of any airway down to subsegmental level. The tip of the bronchoscope is usually kept in the trachea or main bronchus to minimize interference with local ventilation. With a little practice it is

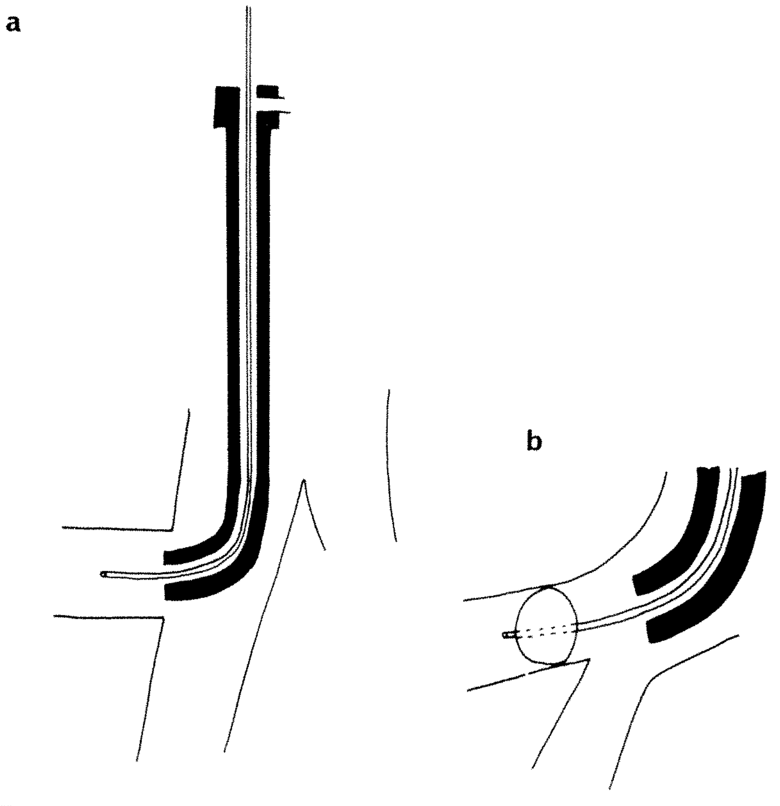


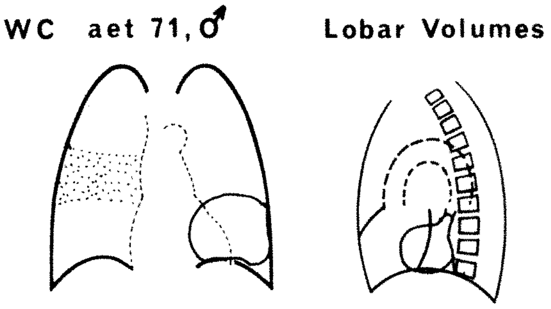
Fig. 6. a, Fibreoptic bronchoscope with mass spectrometer probe in suction channel. *b*, An occlusion catheter with balloon inflated obstructing a bronchus

easy to keep the probe tip in position even during extreme respiratory manoeuvres. If the probe does become blocked with mucus it can be left in situ and its lumen cleared by an injection of 10–20 ml of air from a syringe.

The combination of bronchoscope and sampling probe (Fig. 6*a*) behaves as a double-lumen catheter through which marker gases can be injected and respired gases sampled in a variety of ways. Similarly if a cuffed sampling probe such as a long Swann-Ganz catheter is passed down the suction channel its balloon can be inflated to isolate a lobe of segment and the function of the obstructed and adjacent unobstructed parts of the lung followed separately (Fig. 6*b*)

ACCESSIBLE GAS VOLUME

When a breath is taken the incoming gas is distributed to that part of the lung which the gas can reach, by a combination of bulk flow and diffusion, in the time available. This space is called the accessible gas volume. It is measured from the dilution of any inhaled or resident insoluble gas. This is seen, for example, in the single-breath test of transfer factor (Tl,co) which coincidentally estimates the volume of lung reached by helium in 10 seconds. In normal people this is equivalent to some 95% of total lung volume, but



LOBE	VOL; obsv.	pred.
RUL	761	1891
RML	869	815
RLL	954	2235
LUL & Lingula	1589	1882
LLL	329	2226
Total	4502	9049

Fig. 7. Lobar argon dilution volumes obtained in a man with emphysema and a large bulla in the left lower zone compared with predicted values

in those with obstructive disorders it can be much less. The difference between total and accessible lung volumes is a sensitive index of the degree of obstruction.

We have used two methods to estimate the accessible volumes of lobes and segments during bronchoscopy: the first employs injection of a bolus of argon locally and the second involves transient occlusion of the local airway after argon has been inhaled into the lung generally. In the bolus procedure the patient is asked to expire to residual volume (RV), inspire to total lung capacity (TLC) and then make a slow expiration. During inspiration a 20 ml bolus of argon is injected into the lobar or segmental airway through the sampling probe. Throughout the injection the spectrometer samples gas from the suction channel of the bronchoscope to check whether any of the bolus is lost to other parts of the lung. On expiration the spectrometer is switched to draw gas from the sample probe and to measure the concentration of argon expired locally. Accessible gas volume and inhomogeneity of ventilation are determined from the height and slope of the expired argon plateau respectively. Table I shows the lobar volumes obtained by this method and compares them with the radiographic estimates of his lobar volumes mentioned previously, and with the anatomical data of Horsfield (1967). Fig. 7 shows corresponding measurements made during routine bronchoscopy in a 71-year-old man with a large emphysematous bulla in his left lower lobe. The results show a reduced accessible gas volume in many parts of the lung, especially in the left lower lobe, indicating that little argon has entered the bulla during this manoeuvre.

In the second procedure the patient takes in an argon-marked mixture at the mouth, inspiring from RV to TLC. At TLC the airway of the lobe or segment under study is occluded with a balloon catheter and the patient is asked to breathe out maximally into

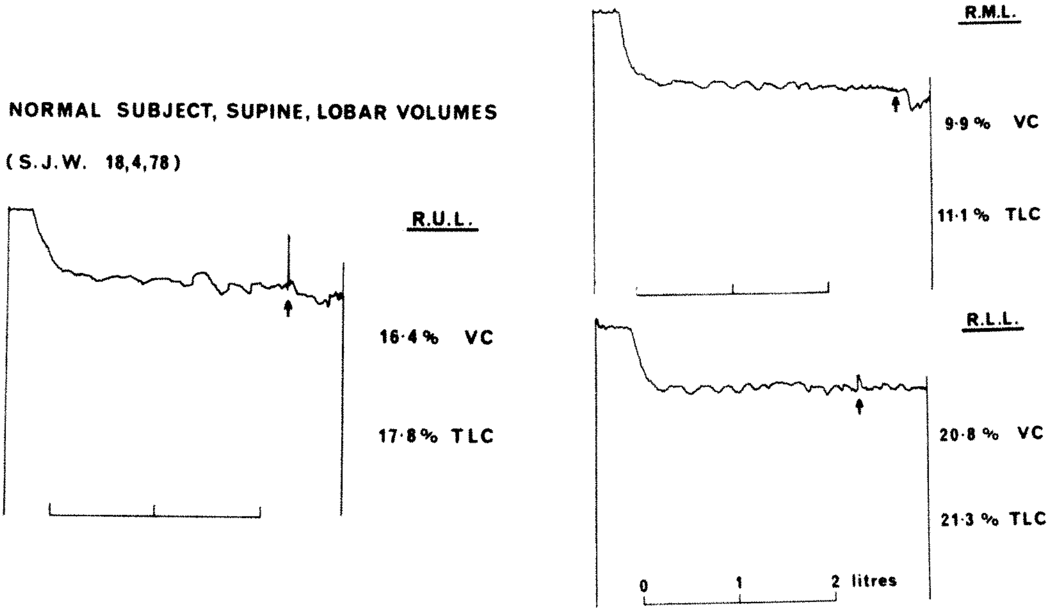


Fig. 8. Trace of argon concentration and volume, obtained by the occlusion technique in each lobe of the right lung in a normal supine subject

a spirometer. Then, while expiratory effort is sustained, the balloon is deflated and the volume and argon concentration expelled from the previously occluded part is measured. Results obtained from a normal subject using this technique are shown in Fig. 8. The vital capacity of each lobe can be read directly from the spirometer and the accessible gas volume can be calculated from the vital capacity and the expired argon concentration.

ALVEOLAR VENTILATION

Whereas, in the lung as a whole, alveolar carbon dioxide pressure reflects the appropriateness of alveolar ventilation to metabolic need, within parts of the lung it is a measure of their ventilation relative to perfusion. West and Hugh-Jones (1959) have described several patterns of expired carbon dioxide trace seen during quiet breathing from parts of the lung. Fig. 9 shows four of these: (*a*) the sharp rise to an almost flat

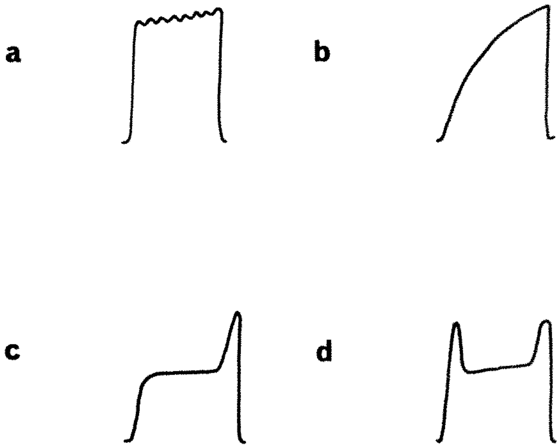


Fig. 9. Four types of expired carbon dioxide traces obtained at bronchoscopy

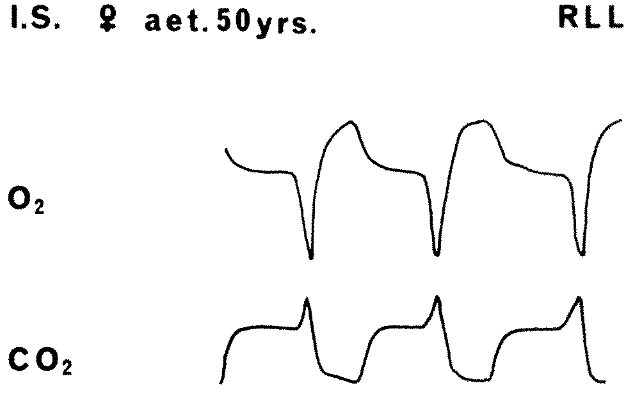


Fig. 10. Oxygen and carbon dioxide tensions recorded from the right lower lobe of a woman with almost complete occlusion of the right main pulmonary artery

alveolar plateau and steep return to inspired air seen in normal breathing; (*b*) the slurred interface between dead-space and alveolar gas when alveolar mixing is poor as in emphysema; (*c*) the low flat plateau with a transient increase at the start of inspiration seen in regions that are poorly perfused relative to their ventilation; and (*d*) a fall in the plateau part of the way through expiration when well and poorly ventilated regions are breathing out of phase.

Fig. 10 shows the oxygen and carbon dioxide tensions recorded during quiet breathing from the right lower lobe of a 50-year-old woman with almost complete occlusion of her right main pulmonary artery. During expiration the alveolar carbon dioxide is low and flat because of the ischaemia but on inspiration the first gas to enter the lower lobe bronchus, from the trachea, is rich in carbon dioxide from the well perfused left lung. Corresponding changes in respired oxygen are more marked because of the wider difference between alveolar and mixed venous $P\text{O}_2$ than $P\text{CO}_2$.

Although the slope of the plateau reflects alveolar mixing and its height is an index of ventilation perfusion (V/Q) ratio other influences such as continuing gas exchange and diminishing lung volume also affect them. When the V/Q ratio is low $P\text{CO}_2$ rises towards mixed venous levels which are not much higher than arterial. When the ratio is high alveolar $P\text{CO}_2$ falls towards inspired values which are substantially lower than arterial. Thus plateau height is more sensitive to a rise than to a fall in V/Q ratio. For all these reasons carbon dioxide traces from parts of the lung may be difficult to compare and interpret with precision.

If at bronchoscopy the patient is turned from air to oxygen during quiet breathing the wash-out of nitrogen can be recorded from any part of the lung, providing an index of the ratio of alveolar ventilation to alveolar volume. Similarly, when the patient returns to breathing air the wash-in of nitrogen can be recorded giving the same information. Fig. 11 is such a record, obtained from the left upper lobe of a normal, supine subject. The lower trace, with constant levels of end-tidal $P\text{CO}_2$, demonstrates that ventilation was steady throughout this procedure.

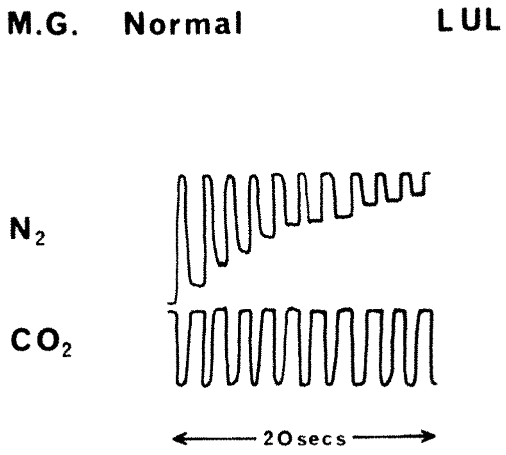
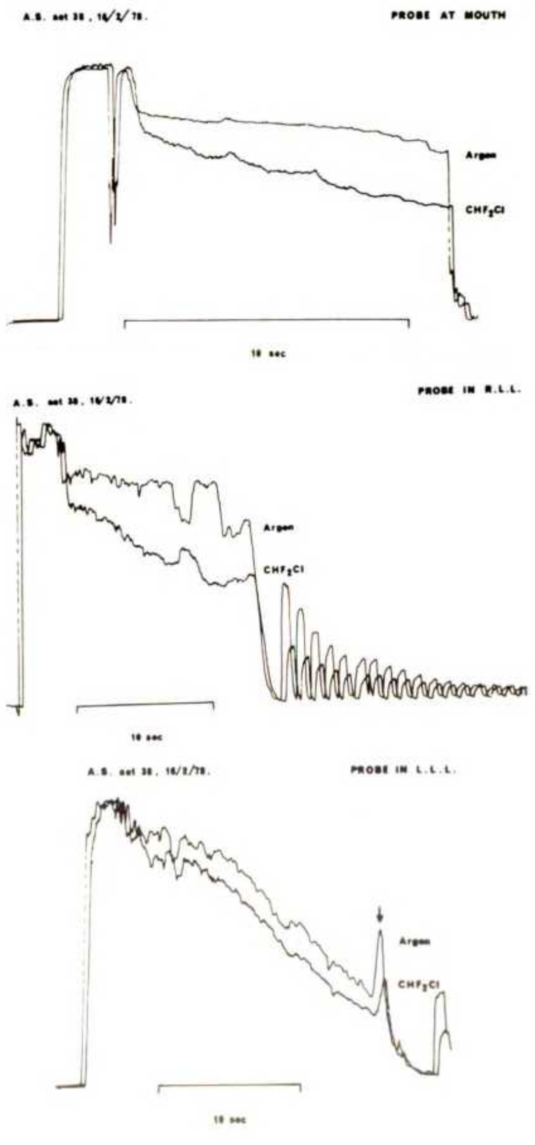


Fig. 11. Nitrogen and carbon dioxide concentrations obtained during wash in of nitrogen after breathing 100% oxygen recorded from the left upper lobe of a normal supine subject



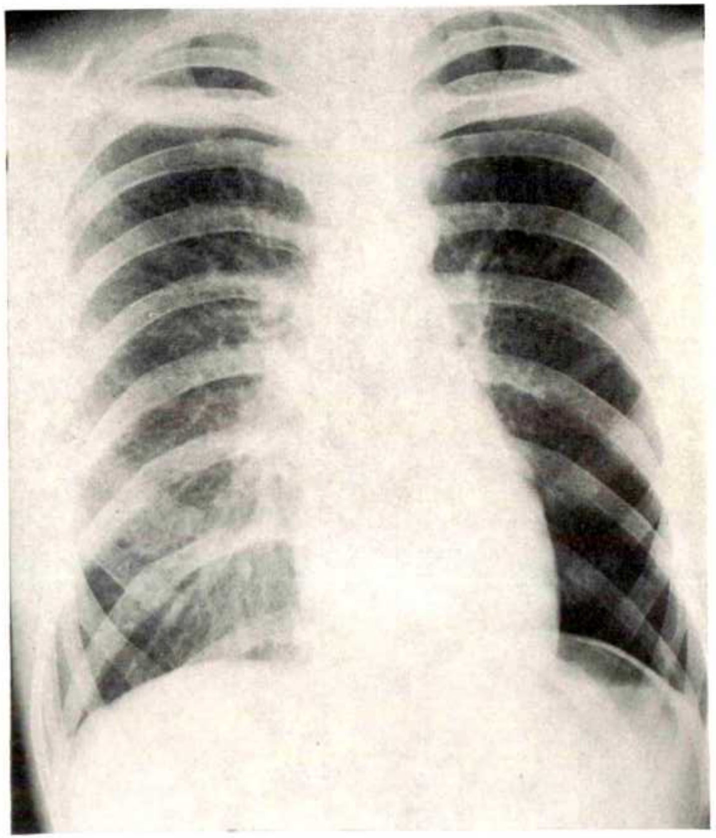


Fig. 12. Plain chest radiograph and spectrometer tracings recorded at the mouth, right lower lobe bronchus and left lower lobe bronchus of a supine 38-year-old man with partial Macleod's syndrome involving his left lower lobe

EFFECTIVE BLOOD FLOW

If a patient inspires air marked with small amounts of two gases, one insoluble and the other soluble in blood, and then expires at a slow and even rate, the different rates of the two gases can be followed by spectrometry. The insoluble gas cannot escape from the lungs to the alveoli so the height and shape of its alveolar plateau are a measure of accessible volume and the evenness of ventilation. By contrast, the soluble gas is carried away by the passing blood stream and thus its concentration during expiration falls continuously. The differences between the two traces are a measure of effective blood flow, that is to say the flow of blood which comes into gas-exchanging contact with respired air (Cander & Forster 1959).

This procedure is easily applied to parts of the lung at bronchoscopy. The patient expires to residual volume and then rapidly inspires air marked with low percentages of argon, which is insoluble, and difluoromonochloromethane (Freon 22), which is as soluble as nitrous oxide. He then holds his breath for a few seconds and breathes out slowly.

This test has been used on many patients and Fig. 12 shows the chest radiograph and spectrometer tracings from one of them: a 38-year-old man with Macleod's syndrome affecting the left lower lobe. The upper tracing, obtained at the mouth, shows an almost flat argon plateau and a concentration of Freon 22 that falls steadily with time. The middle

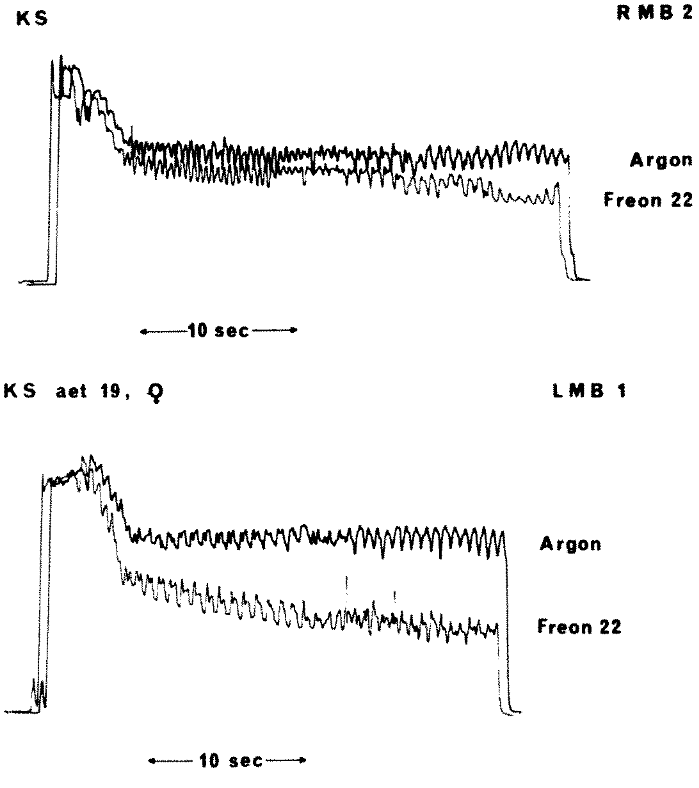


Fig. 13. Argon and Freon 22 tracings recorded in the main bronchi of a supine 19-year-old woman a few weeks after having a large embolus removed from her right main pulmonary artery

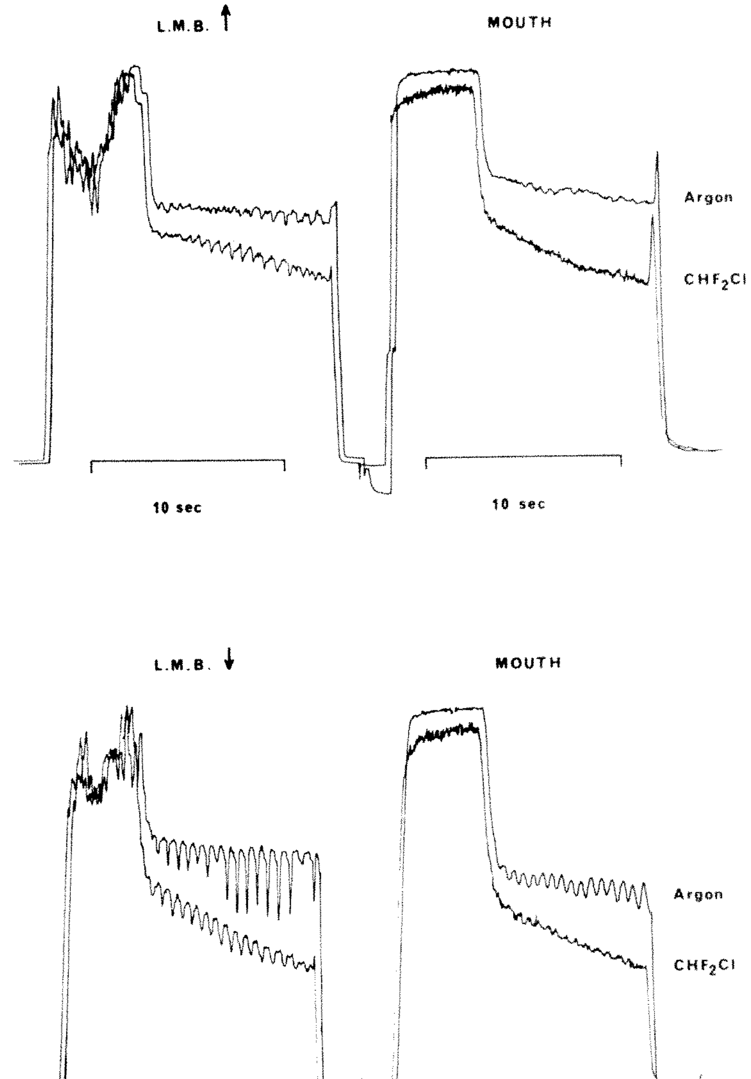


Fig. 14. Argon and Freon 22 tracings obtained from the left main bronchus and at the mouth in a normal subject lying first on his left and then his right side

trace, from the right lower lobe, has much the same form disturbed by cardiogenic oscillations and later by closing volume phenomena. The separation of insoluble and soluble gas concentrations is wider than at the mouth because blood flow per litre of lung volume in the right lower lobe is greater than to the lung as a whole, even though the patient was supine. By contrast the bottom tracing, recorded from the left lower lobe, shows a continuously falling argon concentration because of poor mixing and a constant and narrow separation between argon and Freon 22. The initial fall in Freon concentration is due to its solution in lung water. The absence of any further separation shows that there is no blood flow effective for gas exchange in this lobe. At the point marked by an arrow the subject inspired, drawing in gas from the trachea which delivers gas reflecting the better ventilation and perfusion of the remaining lung.

Fig. 13 shows the argon and Freon 22 traces obtained from each lung in a 19-year-old woman who two months previously had a large thrombus removed from the right main pulmonary artery. Following this she was still quite breathless on mild exertion. The argon trace obtained from the right main bronchus shows that there is even ventilation in that lung but there is no separation of the argon and Freon 22 tracings which indicates that there is no effective pulmonary blood flow in the right lung. In contrast the left lung shows the normal pattern.

The sampling probe commonly used in respiratory mass spectrometry is 1–3 m long and gas entering its tip will arrive at the spectrometer and be analysed about 0.1 second later. If longer probes are used the transit time increases but the waveform is accurately preserved (Davies & Denison 1979). Thus, using probes of different lengths, it is possible to record gas tensions from different parts of the lung in the same breath and examine them in the sequence in which they arrive at the spectrometer. An example of this is shown in Fig. 14 which records the ventilation and effective blood flow to the left lung of a normal subject lying first on his left and then on his right side. The endobronchial record was obtained by a conventional short probe (1 m) passed through the bronchoscope. Tracings of the same breath as seen at the mouth were obtained with a 30 m probe that delayed its arrival at the spectrometer by 18 seconds. The tracings show how the increased ventilation and blood flow of the dependent lung, and the reduced ventilation and blood flow of the upper lobe, combine to give an intermediate trace at the mouth. Thus parts of the lung can be compared with each other, within the same breath, by using sample probes of different lengths.

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AN ANALYSIS OF THE FIRST 300 FIBREOPTIC BRONCHOSCOPIES AT THE BROMPTON HOSPITAL

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Summary

We report the results of the first 300 fibreoptic bronchoscopies carried out at the Brompton Hospital. Positive cell typing was possible in only 36% of the visible carcinomas in the first 150 patients, but in 74% of the second 150. The reasons for this difference are discussed.

We suggest that fibreoptic bronchoscopy be carried out in district referral hospitals where sufficient experience can be gained to produce good results. Our results suggest that the trap specimen should be examined routinely for acid-fast bacilli, for malignant cells only if biopsy is negative and not at all for other bacteria.

With experience good results can be obtained by physicians and the expertise gained is invaluable in the investigation and treatment of a wide range of patients, many of whom do not need surgical treatment.

Introduction

Fibreoptic bronchoscopy was introduced in Japan in 1967 (Ikeda et al. 1968) and subsequently used throughout America (Sackner 1975). Although a number of centres have begun to use this technique in this country, there remains some doubt as to where it should be done, by whom and, even, if at all. In this analysis of the first 300 patients investigated by fibreoptic bronchoscopy at the Brompton Hospital we hope to offer answers to these questions.

Methods

Bronchoscopy

We have described our technique in full elsewhere (Clarke & Knight 1977). The patients were fasted for four hours and after premedication with Omnopon and Scopolamine brought to the bronchoscopy room. After local anaesthesia the bronchoscope was passed transnasally with the operator in front of the patient. The tracheobronchial tree was examined systematically and the aspirated secretions collected in a trap bottle included in the suction line. Visible abnormalities were biopsied under direct vision using the small forceps, up to three or four biopsies being taken from each lesion.

After bronchoscopy the patients rested for 60–90 minutes to allow the local anaesthesia to wear off. They were then allowed to eat and drink and after a few hours could be allowed home, accompanied, if admitted to the Day Ward.

Trap specimen

This was divided into two. One specimen was centrifuged and wet preparations made from the deposits. These were stained with methylene blue and examined for malignant cells. The other specimen was homogenized with glass beads. Samples were incubated aerobically, anaerobically, under CO_2 and on a MacKonkey plate. The remainder was examined for acid-fast bacilli using an adapted Petroff's method and cultured on Lowenstein–Jensen slopes.

Biopsies

Samples of tissue were placed immediately into 10% neutral buffered formalin solution and fixed for a minimum of 15 min. The biopsies were processed by hand in the small (15 ml) bottles into which they were initially placed. To enable easy recognition of the small tissue fragments, they were pre-stained in picric acid. Formalin was removed from the specimen using a Pasteur pipette and the biopsies immersed in a saturated solution of picric acid in 90% alcohol for 20 min each. The specimens were then cleared in xylene for 20 min and impregnated with molten paraffin wax for 1 hour. They were embedded, cut at three levels and stained with haematoxylin and eosin.

Sterilization

The working length of the bronchoscope, biopsy forceps, brushes and connectors were cleaned in running tap water and then sterilized in activated glutaraldehyde for 20 min.

RESULTS

We have divided our results into two series: 1–150 and 151–300. This was done to see whether any change occurred in the type of patient put forward for bronchoscopy and in the results obtained as we developed our service.

Patients

The age and sex distribution was remarkably consistent in the two series (Table I) as were the presenting symptoms (Table II) and chest radiograph findings (Table III). The indications for fibreoptic bronchoscopy are shown in Table IV. Two headings in this table require explanation. The heading 'fuller examination required' refers mainly to patients with haemoptysis and normal or unchanged chest radiographs in whom the fullest possible survey was required to try to find the site of bleeding. In those patients in whom 'dynamic observations' were required, we were asked to see whether there was abnormal collapsibility or rigidity of the tracheobronchial tree during voluntary manoeuvres such as coughing and deep breathing.

Table I. Patients

	No. 1–150	*No.* 151–300	*Total*
Males	102	99	201 (67%)
Females	48	51	99 (33%)
Age (mean and range)	57 (18–83)	57 (19–84)	57 (18–84)

Table II. Presenting symptom

Symptom	*No.* 1–150*	*No.* 151–300†	*Total*
None	7	2	9 (3%)
Cough	62	53	115 (38%)
Sputum	52	22	74 (25%)
Blood	52	56	108 (36%)
Pain	35	47	82 (27%)
Shortness of breath	43	38	81 (27%)
Wheeze	15	6	21 (7%)
Malaise	13	8	21 (7%)

* Other symptoms: weight loss (6), superior vena cava obstruction (3), night sweats (2), voice change (2), malignant cells in sputum (2), bronchopulmonary aspergillosis (2), adenocarcinomatosis (1), clubbing (1), acanthosis nigricans (1), peripheral neuropathy (1), mitral stenosis (1), arthralgia (1).

† Other symptoms: weight loss (8), voice change (4), night sweats (3), bronchopulmonary aspergillosis (3), neurological symptoms (2), malignant cells in sputum (2), Addison's disease (1), stridor (1), thyrotoxicosis (1), mycosis fungoides (1), hypertrophic pulmonary osteoarthropathy (1).

Table III. Chest radiograph findings

Finding	*No.* 1–150*	*No.* 151–300†	*Total*
Normal	17	16	33 (11%)
Mass	30	35	65 (22%)
Collapse	30	21	51 (17%)
Shadow	72	63	135 (45%)
Effusion	5	13	18 (6%)
Old pulmonary tuberculosis	19	17	36 (12%)

* Other findings: cavity (4), nodes (2), mycetoma (1), pleural plaques (1), cardiac failure (1), active pulmonary tuberculosis (1).

† Other findings: nodes (4), cavity (2), mycetoma (2), active pulmonary tuberculosis (1), pneumothorax (1), 'honeycombing' (1).

In the majority of the carcinoma patients sputum cytology was negative or there was no sputum. Patients with positive sputum cytology findings were examined by bronchoscopy only if the site of the carcinoma was unknown.

Bronchoscopic findings

After each case, a report was written on a form that we found suitable. The bronchoscopic appearances are summarized in Table V. The second series contained more patients with carcinoma and also more patients with mucus plugging of the bronchial tree.

Table IV. Indications for fibreoptic bronchoscopy

Indication	*No.* 1–150	*No.* 151–300	*Total*
Outside range of rigid bronchoscope			
Upper lobe	45	69	114 (38%)
Elsewhere	33	29	62 (21%)
Previous rigid bronchoscopy negative	14	6	20 (7%)
Fuller examination required*	62	38	100 (33%)
Poor anaesthetic risk	4	2	6 (2%)
Tracheal stenosis	2	2	4 (1%)
Severe kyphosis	1	—	1 (0.3%)
Dynamic observation required*	4	4	8 (3%)

* For details see text.

Table V. Visual diagnosis

Diagnosis	*No.* 1–150*	*No.* 151–300†	*Total*
Normal	35	31	66 (22%)
Tumour	31	46	77 (26%)
Inflammation	49	35	84 (28%)
Stenosis	13	14	27 (9%)
Secretion	4	1	5 (2%)
Crowding/distortion	5	5	10 (3%)
Mucus plugging	1	8	9 (3%)
Blood localized	6	3	9 (3%)

* Also diagnosed: tuberculosis (1), tracheobronchomegaly (1), bronchial adenoma (1), endobronchial sarcoid (1), irritable airways (1).

† Also diagnosed: extrinsic compression (3), tuberculosis (2), tracheopathia osteoplastica (1), mycetoma (1).

Biopsy and trap results

The biopsy results are summarized in Table VI. In an attempt to determine the diagnostic usefulness of the biopsy and of trap cytology, we have analysed the results obtained in those patients in whom a visible abnormality was seen at bronchoscopy and in whom the final diagnosis was carcinoma (Table VII). We chose to consider visible lesions only in order to make comparison with other published series, in particular those carried out using the rigid bronchoscope.

In the second series, in which a positive cell type was determined by examination of the biopsy material in 74%, the histological diagnosis was squamous cell carcinoma (82%) and oat cell carcinoma, adenocarcinoma and undifferentiated carcinoma 6% each.

Trap cytology

The results for patients with visible carcinomas have been mentioned. There were two patients with positive cytology and no visible tumour. One subsequently underwent pneumonectomy and histology revealed a poorly differentiated squamous carcinoma in the

Table VI. Biopsy results

Result	*No.* 1–150*	*No.* 151–300†
Normal	43	33
Tumour	25	45
Inflammatory	18	13
Squamous metaplasia	8	5
Sarcoid	2	1
Tuberculosis	1	5

Brush biopsy: 65 negative cytology; 1 positive cytology.

* Also found: thickening of basement membrane (2), keratizing squamous epithelium (1), normal lung (1), stratification of mucosa (2), not processed (1).

† Also found: dropped in transit (1), disintegrated in fixative (1), mycelium (1), bronchopulmonary aspergillosis (1), ossification in the mucosa (1).

Table VII. Results for visible carcinomas

Result	*No.* 1–150 ($n=29$)		*No.* 151–300 ($n=47$)	
	Biopsy	Trap	Biopsy	Trap
Positive cell type	10 (36%)	1 (7%)	35 (74%)	7 (16%)
Probable cell type	7 (25%)	1 (4%)	7 (15%)	9 (20%
Suggestive of carcinoma	6 (21%)	—	3 (6%)	1 (2%)
Negative	5 (18%)	24 (89%)	2 (4%)	27 (61%)
Not done	1	2	—	3

lower lobe. The second patient was investigated for right upper lobe shadowing found on a routine chest radiograph. Both squamous cells and tubercle bacilli were found in his sputum. Bronchoscopy was normal and he remains well with negative sputum cytology findings and normal findings on repeat of bronchoscopy 15 months after the first examination.

For visible lesions trap cytology revealed ‘probably malignant’ cells in the 4% of the second series in which the biopsy findings were negative.

Bacteriology of trap specimens

Tubercle results. A positive culture for tubercle bacilli was obtained in seven patients. Two were examined by bronchoscopy whilst on treatment for tuberculosis as there was a strong suspicion of coexisting carcinoma. Both bronchoscopies were normal. Two patients had upper lobe shadowing; one who presented with Addison’s syndrome was examined by bronchoscopy twice. In both mucosal biopsies showed tuberculous lesions. Three patients had unsuspected tuberculosis. One had a radiologically opaque hemithorax and at bronchoscopy a lymph node was found ulcerating into the lower end of the trachea. The significance of the finding of tubercle bacilli in two patients is not clear as one died from the oat-cell carcinoma, also diagnosed at bronchoscopy, and the second remains well after an upper lobectomy for carcinoma having received no anti-tuberculous drugs.

Two patients had a positive smear and negative culture. One patient had tracheobronchomegaly and no evidence of tuberculosis. The other patient, a man with old tuberculosis, had squamous cells in his sputum. No carcinoma was seen at bronchoscopy and he gained weight on anti-tuberculous therapy. He subsequently developed pleural effusion and repeat bronchoscopy showed a left lower lobe carcinoma later removed by pneumonectomy.

Bacteriology. Two hundred and forty traps specimens were examined: 92 (38%) were reported as sterile and 135 (55%) as 'no pathogens isolated'. The latter report was given when nasopharyngeal commensals only were isolated. Eighteen pathogens were isolated: *Staph. aureus* in 10 patients, *Pseudomonas aeruginosa* in six, *Str. pneumoniae* in one and *Haemophilus influenzae* in one. In all patients with *Pseudomonas*, the organism had been isolated previously from the sputum. Of the 10 patients with staphylococci in the trap, four had had previous isolation from the sputum. There was subsequent isolation in two from a nasal swab and in another from the sputum. In two patients, no further specimens were examined. In one patient who had undergone fibreoptic bronchoscopy one week before only a trap specimen was examined with negative findings on that occasion—subsequently nasal swab findings were positive.

Aspergillus fumigatus was isolated from four patients; three had allergic bronchopulmonary aspergillosis (one previously undiagnosed). The other isolation was from a patient in whom a previously unsuspected mycetoma was diagnosed. Biopsy of endobronchial mycelium in the latter patient also yielded a growth of *Aspergillus fumigatus.*

Brush biopsy

This yielded only one positive result for carcinoma. This technique was used only for lesions that could not be seen, and as fluoroscopy was not used in this initial series of patients it is not surprising that the yield was rather poor.

DISCUSSION

In our second series there were more patients with carcinoma and with mucus plugging of the bronchial tree. We believe that the greater number of carcinoma patients reflects a growing awareness of the usefulness of the technique, particularly for upper lobe lesions, amongst our colleagues. This is shown also by the general increase in numbers of patients referred. Fibreoptic bronchoscopy was used therapeutically to aspirate mucus plugs in patients with bronchopulmonary aspergillosis. Our initial experience was encouraging and one bronchoscopy was usually enough to allow reinflation of segments and lobes (Knight 1979).

The trap specimen contains all secretions removed through the centre channel of the bronchoscope during the procedure. This was contaminated with nasopharangeal commensals in 55% of examinations. We therefore agree with others (Bartlett et al. 1976) that routine culture of this trap material is unhelpful. If a bacteriological diagnosis is required then other techniques should be used such as transtracheal aspiration

(Hoeprich 1970) or selective culture using a sheathed brush or wire loop passed through the centre channel of the fibreoptic bronchoscope (Wanner et al. 1973). All trap specimens, however, should be examined directly and cultured for tubercle bacilli. Mycological examination is useful in selected cases. In our first 300 cases, this resulted in the previously unsuspected diagnosis of pulmonary aspergillosis in two patients, including one patient with a mycetoma not apparent on the chest radiograph. Routine examination for malignant cells is time consuming and added little further information in our series; we suggest that this is done only if a malignant condition is suspected and the biopsy is negative.

The biopsy results are, in the main, self-explanatory and we will discuss only the carcinoma results. Ikeda et al. (1968) put forward specifications for a fibreoptic bronchoscope in order to try and make the diagnosis of bronchial carcinoma at an early stage and thus, it was hoped, improve long-term survival. The fibreoptic bronchoscope has considerably extended the area of the bronchial tree available for direct inspection and biopsy compared with rigid bronchoscopy (Kovnat et al. 1974). This alone is justification for the instrument. The diagnostic usefulness of the biopsy, however, has been questioned owing to its small size (approximately 2 mm^3). Small forceps have the advantage, however, that they can be passed into peripheral bronchi. For more central lesions the minimal trauma produced means that three or four biopsies can be taken from one site. In the second 150 patients there was a dramatic improvement in the number of visible tumours in which cell typing was possible from the biopsy material (74% compared with 36% in the first series). The same type of forceps was used throughout and there was no change in the handling of specimens. We believe that this improvement reflects changes both in biopsy technique and in the interpretation of the biopsies by our pathologist. If necrotic areas of tumour are sampled the results will be poor. With experience suitable areas may be chosen and the presence of a little bleeding after biopsy is helpful as it means that viable tissue has been sampled. The small biopsies are often crushed by the forceps, a feature making interpretation difficult for the novice.

Our experience is thus similar to that of Oho et al. (1975) who found that their positive biopsy findings rate improved from 80% in 1971 to 97% in 1974. In two British series the positive biopsy rates for *visible* tumours using the rigid bronchoscope (Somner et al. 1958) and the fibreoptic bronchoscope (MacDonald 1975) were identical, 94%. Both these series and Oho et al. (1975) do not say what they mean by 'positive' and do not describe the precise pathological interpretation of their biopsies. In our hands in the second 150 patients positive diagnosis of carcinoma was obtained in 89% of biopsies of visible lesions. A further 6% were suggestive of carcinoma, but not diagnostic; and 4% were negative. In the two patients with negative findings trap cytology suggested carcinoma. By positive we mean a certain diagnosis of carcinoma. Although this is very useful information alone, accurate cell-typing of the tumour may assist selection of therapy and prediction of prognosis. In the second series cell typing was possible in 74% of the patients with visible carcinoma.

All our bronchoscopies were carried out in a small room with the aid of one staff nurse. As we do not depend on theatre time or require anaesthetists, we are able to bronchoscope patients at very short notice (occasionally the same day as they present). Many of our patients have conditions that do not require surgery. The number of bronchoscopies that we now carry out (up to 80/month) and the time each may take (up to one hour) means that already busy surgical facilities would be overloaded if patients were so referred. Our results and those of others suggest that good results can be obtained by physicians. The experience we have gained in our exploration of the normal and abnormal bronchial tree has been a particular help in increasing our understanding of the physiology and pathology of the lung.

We believe that fibreoptic bronchoscopy is a great advance in methods for the diagnosis and management of pulmonary disease. The technique, however, requires skill and experience if it is to be carried out with minimal discomfort for the patient and maximum diagnostic and therapeutic value. Our experience suggests that a period is necessary during which the biopsy results are improved by the experience of the operator and pathologist. In view of these facts, it may well be that fibreoptic bronchoscopy should be used to diagnose carcinoma (and perhaps other lesions) in district referral hospitals only if sufficient numbers of patients will provide the experience which is essential for good results.

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DOUBLE-BLIND TRIAL COMPARING TWO DOSAGE SCHEDULES OF BECLOMETHASONE DIPROPIONATE AEROSOL WITH A PLACEBO IN CHRONIC BRONCHIAL ASTHMA

SECOND REPORT OF THE BROMPTON HOSPITAL/MEDICAL RESEARCH COUNCIL COLLABORATIVE TRIAL*

Summary

A follow-up study to 52 weeks is reported on 95 corticosteroid-dependent asthmatics who took part in a double-blind, controlled trial of beclomethasone dipropionate for 28 weeks. During the 28 weeks two dosage schedules (800 μg and 400 μg daily) were compared with a placebo. If the corticosteroid tablet dosage had been at least halved and the clinical condition was satisfactory, the allocated regimen was continued 'blind' for the second period (29–52 weeks); 51 patients continued for this period, 46 on beclomethasone dipropionate. If progress was unsatisfactory, known beclomethasone dipropionate 800 μg daily was substituted, the supervision remaining unchanged, the clinical supervisors remaining unaware which schedule had been received during the first 28 weeks. Nearly all the patients who at least halved their corticosteroid tablet dosage by 28 weeks continued to do well up to 52 weeks on the allocated regimen. When the placebo patients with unsatisfactory progress at 28 weeks were changed to 800 μg beclomethasone dipropionate they showed a substantial improvement. Patients changed from 400 to 800 μg showed little improvement on average. Approximately 30% of the whole group of patients failed to halve their dosage of corticosteroid tablets, despite receiving 800 μg beclomethasone dipropionate daily for six or more months.

The cumulative incidence of 'oral candidiasis' (as defined for this report) in placebo patients changed at 28 weeks to 800 μg beclomethasone dipropionate daily was 30% at 36 weeks and 43% at 52 weeks. Of eight patients increased from 400 μg to 800 μg daily, one had 'candidiasis' by 36 weeks and three by 52 weeks. Oral candidiasis was often asymptomatic and never led to the discontinuation of the corticosteroid aerosol, although the dosage was reduced in nine of the 30 who received 800 μg beclomethasone dipropionate during the first 28 weeks. The incidence of bacterial infections in patients on beclomethasone dipropionate was similar to that of the placebo group and systematic laboratory investigations revealed no increase in the rate of isolation of potential pathogens.

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* The trial was coordinated by R. M. Cayton, C. A. Soutar, C. F. Stanford, G. C. Turner (of the Brompton Hospital, London) and A. J. Nunn (of the Medical Research Council Tuberculosis and Chest Diseases Unit, London). Supervisors were Margaret Turner-Warwick and T. J. H. Clark (Brompton Hospital) and Wallace Fox (MRC). Collaborating physicians were: J. R. Bignall, T. J. H. Clark, H. Nicholson, N. C. Oswald, J. Pepys, K. Robson, F. H. Scadding, J. Smart and M. Turner-Warwick (of the Brompton Hospital). This report was written by R. M. Cayton (now at the East Birmingham Hospital) and A. J. Nunn, together with the supervisors of the trial.

INTRODUCTION

A preliminary report (Brompton Hospital/Medical Research Council 1974) showed that, as assessed for six months in a double-blind trial, 400 μg beclomethasone dipropionate daily was therapeutically effective in many patients taking 15 mg prednisone or less daily, but that in some patients taking 16 mg or more daily an 800 μg dosage was more effective. However, by the criteria used a high cumulative incidence of oropharyngeal candidiasis was associated with inhaled beclomethasone dipropionate; 77% of the patients on 800 μg and 45% of those on the 400 μg dosage were affected, compared with 9% receiving the placebo aerosol This report confirms the initial findings and presents additional data concerning the long-term efficacy and side effects of beclomethasone dipropionate.

Materials and Methods

Details of the patients and procedures have been described in the earlier report (Brompton Hospital/Medical Research Council 1974). In brief, all patients were over 16 years of age and had asthma of sufficient severity to warrant treatment with corticosteroid tablets for the previous six months or more in doses equivalent to at least 5 mg prednisone daily. No patient had previously been treated with beclomethasone dipropionate or was receiving corticotrophin (ACTH) on admission to the study.

Allocation of treatment

Each patient was studied for 56 weeks, which included a four-week pre-trial assessment period and 52 weeks in the trial. The patients were grouped according to the mode of their daily dosage of prednisone (5–9 mg, 10–15 mg and 16 mg or more) during the last two weeks of the pre-trial period and then allocated at random to the dosage schedules shown in Table I.

Beclomethasone dipropionate was administered as an aerosol from a pressure-packed can delivering a dose of 50 μg per puff. The placebo contained only propellant gas and oleic acid, a wetting agent.

Duration of treatment

The first 28 weeks of the trial were conducted double-blind; the identity of the trial aerosol was unknown to the patient, to the clinical assessor and to the physician in charge. Each patient's treatment was reviewed at 28 weeks. If the patient had succeeded in reducing the mode of his daily dosage of prednisone to half the starting dosage or lower by 28 weeks, the protocol recommended the continuation of the allocated trial aerosol. Patients in whom such an improvement had not been

Table I. Dosage schedules

Series	*Agent*	*No. of inhalations**	*Total daily dosage of active agent* (μg)
B4	Beclomethasone dipropionate	4 puffs	800
B2	Beclomethasone dipropionate	2 puffs	400
P4	Placebo	4 puffs	—
P2	Placebo	2 puffs	—

* Four times a day.

achieved were given known beclomethasone dipropionate (800 μg daily), but neither the physician nor the clinical assessor were informed of the regimen the patient had been receiving during the first 28 weeks.

Organization of the trial and assessment of asthma

The patients attended special out-patient sessions at monthly intervals. At each attendance, the forced vital capacity (FVC) and forced expiratory volume (FEV_1) were measured with a bellows spirometer (Vitalograph) before and five minutes after the inhalation of 400 μg isoprenaline sulphate. The patient was then seen and examined by the clinical assessor who, with the aid of a diary of asthma symptoms recorded daily by the patient, judged the severity of the asthma and assessed the need to adjust the dosage of prednisone.

Because of the hazards of unrecognized adrenal insufficiency patients were instructed to reduce their dosage of prednisone slowly, at a maximum rate of 2.5 mg per week if taking more than 5 mg prednisone daily and 1 mg per week, if taking less. Patients were instructed to increase the dosage of prednisone if their asthma worsened or if they suffered corticosteroid withdrawal symptoms such as nausea, lethargy, malaise or weakness.

Investigations for oropharyngeal candidiasis

Investigations for oropharyngeal candidiasis were by both systematic clinical observations and routine throat swab cultures. The patient's mouth and pharynx were inspected at each attendance and the presence of candidiasis was recorded when erythema plus discrete or confluent white patches were present. Initially throat swabs were taken only in those patients who developed oropharyngeal candidiasis. However, as the trial progessed it became apparent that many patients were developing such oral candidiasis. Throat swabs were thereafter taken routinely at every attendance and cultured for fungi as described in the 1974 report (Brompton Hospital/Medical Research Council). In some patients, despite the presence of discrete white patches on the mouth and/or pharynx, the visual diagnosis was recorded as being 'in doubt', usually because they were few in number or very small in size; reference was then made to the throat swab culture taken at the same time and *only* if it grew 20 colonies or more was the episode included as 'oral candidiasis' in the analyses. Thus, in this report all patients classified as having 'oral candidiasis' had either (*a*) a definite visual diagnosis or (*b*) a doubtful visual diagnosis with a colony count of 20 colonies or more (a positive culture alone has not been classified as 'oral candidiasis').

Sputum bacteriology

Sputum samples were collected at each attendance, when possible, but some patients sent samples from home. The sputum was graded as mucoid, mucopurulent or purulent. Gram stain and culture were performed and antibiotic sensitivities determined. In this analysis the organisms have been classified as conceivably pathogens or common commensals.

Cytology

Throat scrapings were taken routinely at each attendance. Slides prepared from both sputum samples and throat scrapings were examined for desquamated cells, after fixing with Schaudinn's solution and staining with haematoxylin and eosin.

RESULTS

Patients

Between November 1972 and November 1973, 108 (35 in B4, 38 in B2, 17 in P4 and 18 in P2) patients were admitted to the trial. Seven patients were excluded for reasons given in the 1974 report. A further six (three B4, two B2, one P2) have been excluded between 28 and 52 weeks; one (B4) was given known beclomethasone dipropionate for an acute attack and five stopped taking their aerosol or attending the clinic. Analyses not presented here showed that the P4 and P2 series were similar. They have therefore been combined and will be referred to as the P series. Thus, the data presented are based on the results for 95 patients (30 in B4, 33 in B2 and 32 in P).

At 28 weeks the aerosol dosage was reduced but not stopped in 10 patients (nine B4 and one B2) who had extensive visual 'oral candidiasis'. All 10 patients had already stopped their oral prednisone; only the B2 patient had to resume oral steroids later.

Prednisone reduction

Table II shows the reduction in daily dosage of prednisone achieved in all the patients up to 28 weeks and in those patients who continued on the allocated trial regimen blind up to 52 weeks. Table III shows the progress between 28 and 52 weeks of the patients who were changed to known beclomethasone dipropionate (800 μg daily) because their improvement in the first 28 weeks was unsatisfactory (all but three of the 44 patients had failed to halve their prednisone dosage by 28 weeks).

Considering the 5–9 mg prednisone group in Table II, the B4 patients did well, all 12 continuing the allocated aerosol throughout the 52 weeks. This improvement was maintained, even though seven had a reduced aerosol dosage from 28 weeks, because of persistent 'oral candidiasis'. The B4 patients fared rather better than the 17 B2 patients, three of whom did not continue beyond 28 weeks; the mean percentage reduction in the B4 patients at 52 weeks was 82% and for the B2 patients 58%. In the 10–15 mg group

Table II. Reduction in daily dosage of prednisone achieved in all patients at 28 weeks and at 52 weeks also in those continuing to receive their trial aerosol 'blind' throughout the period

Daily dosage of prednisone on admission (mg)	*Series*	*No. assessed at 28 weeks*	*Mean reduction at 28 weeks* (%)	*No. with unsatisfactory response* at 28 weeks*	*No. continuing to receive trial aerosol 'blind' up to 52 weeks*†	*Reduction in prednisone dosage*					
						Stopped competely		*At least halved*		*Mean reduction* (%)	
						28 weeks	52 weeks	28 weeks	52 weeks	28 weeks	52 weeks
5–9	B4	12	88	0	12 (7)	8	9	11	10	88	82
	B2	17	59	3	14 (1)	7	7	10	8	66	58
	P	12	10	12	0	—	—	—	—	—	—
10–15	B4	13	66	2	11 (2)	3	3	9	11	76	74
	B2	10	64	3	7	0	0	7	4	75	50
	P	14	28	10	4	1	1	3	4	64	79
16 or more	B4	5	59	3	2	0	0	2	1	83	45
	B2	6	18	6	0	—	—	—	—	—	—
	P	6	26	5	1	0	0	1	1	82	76

* See text.

† Figures in parentheses indicate the number of patients whose aerosol dosage was reduced from 28 weeks due to oral candidiasis (see text for details).

Table III. Reduction in daily dosage of prednisone achieved at 52 weeks in patients whose response at 28 weeks was unsatisfactory and whose trial aerosol was changed at 28 weeks to known 800 μg beclomethasone dipropionate (the dosage of the B4 schedule)

Daily dosage of prednisone on admission (mg)	*Initial series*	*No. assessed*	*Mean reduction at 28 weeks* (%)	*Reduction in prednisone dosage at 52 weeks*		
				Stopped completely	*At least halved*	*Mean reduction* (%)
5–9	B2	3	23	0	1	20
	P	12	10	5	8	61
10–15	B4	2	10	0	0	22
	B2	3	40	0	2	39
	P	10	14	2	8	68
16 or more	B4	3	43	0	3	74
	B2	6	18	1	2	36
	P	5	15	0	2	39

the B4 and B2 patients responded similarly at 28 weeks, but the B4 patients proved better able to maintain this improvement; the mean percentage reduction in prednisone dosage at 52 weeks was 74% in the B4 and 50% in the B2 patients. Although in the 16 mg or more group, the B4 patients had the better response up to 28 weeks, the benefit was not maintained in the two patients who continued to 52 weeks. In contrast to the B4 and B2 series the P series had a much less satisfactory response, only five of 32 continuing on the initially allocated regimen beyond 28 weeks.

The most striking finding in Table III, which shows patients who received known 800 μg beclomethasone dipropionate daily (the dosage of the B4 schedule) from 28 weeks, is the benefit to the P series, especially those in the 5–9 mg and 10–15 mg prednisone groups on admission. Of the total of 12 patients changed from the B2 schedule, one stopped prednisone completely and five at least halved their dosage; the corresponding findings for five B4 patients were that none stopped prednisone and three at least halved their dosage.

Spirometric measurements of respiratory function

Table IV compares the percentage reduction in prednisone dosage with the change in the percentage predicted values of the FEV_1 ($FEV_1\%$). The results have been amalgamated because the three series behaved similarly. There was little change in the $FEV_1\%$ in patients at 28 weeks or at 52 weeks, in those patients who continued the trial aerosol blind. The reduction in prednisone dosage was thus achieved without deterioration in spirometry.

Incidence of oral candidiasis

Table V shows the cumulative incidence of 'oral candidiasis' (as defined above) in patients who received the trial aerosol for 52 weeks blind. The subsequent occurrence of 'oral candidiasis' in patients who were changed to 800 μg beclomethasone dipropionate daily (that is, the B4 dosage) at 28 weeks is shown in Table VI after excluding patients in whom a diagnosis had already been made. The colony counts have been given in both tables.

Table IV. Changes in percentage of predicted values of FEV_1 at 28 weeks in all patients and at 52 weeks, for the patients who continued to receive their trial aerosol blind, according to prednisone dosage on admission and the percentage reduction in prednisone dosage achieved by 28 weeks

Daily dosage of prednisone on admission (mg)	*Reduction in prednisone at 28 weeks* (%)	*No. assessed*	*Mean* FEV_1%		*No. continuing to receive trial aerosol blind to 52 weeks*	*Mean* FEV_1%	
			On admission	*At 28 weeks*		*At 28 weeks*	*At 52 weeks*
5–9	0–49	19	72	75	5	87	86
	50–99	7	76	82	6	80	76
	100	15	68	81	15	81	84
10–15	0–49	18	62	58	3	64	58
	50–99	15	68	69	15	69	73
	100	4	56	60	4	60	71
16 or more	0–49	12	45	45	0	—	—
	50–99	5	56	51	3	65	79

Table V. Cumulative incidence of oral candidiasis in patients who continued on their initial trial aerosol blind (for 52 weeks for the B4 and B2 series and for 28 weeks for the P series)

Series	*No. assessed**	*Cumulative incidence of candidiasis*			*Visual diagnosis and colony count on culture*					
					Definite		*Doubtful*		*None*	
		Week 8	*Week 28*	*Week 52*	20 or more	19 to 0	20 or more	19 to 0§	20 or more§	19 to 0§
B4	23	12 (52%)‡	21 (91%)‡	21 (91%)‡	19	1	1	0	0	2
B2	20	7 (35%)‡	10 (50%)‡	11 (55%)‡	7	0	4	1	1	7
P	31†	1 (3%)	3 (10%)	—	0	0	3	3	2	23

* Four (two B4, one B1, one P) patients with oral candidiasis seen by the physician on admission have been excluded.

† Only two P patients without previous candidiasis continued on their trial aerosol blind to 52 weeks; neither were reported as having candidiasis.

‡ Percentages based on less than 25 observations.

§ Not classified as having oral candidiasis.

In the B4 series (Table V) 21 of 23 (91%) and in the B2 series 10 of 20 (50%) patients had at least one episode of 'oral candidiasis' during the first 28 weeks. Neither of the remaining B4 and only one more of the B2 patients developed 'oral candidiasis' later. 'Oral candidiasis' was diagnosed in three of 31 P patients by 28 weeks.* There is a close correlation between the visual and mycological findings.

* The number of patients assessed and the incidences of 'oral candidiasis' by 28 weeks are slightly different from those given in the first report because six (three B4, two B2, one P) patients have been excluded between 28 and 52 weeks and 16 (five B4, 11 B2) patients received known 800 μg beclomethasone dipropionate from 28 to 52 weeks.

Table VI. Cumulative incidence of 'oral candidiasis' in patients who received known 800 μg beclomethasone dipropionate (as in B4 schedule) from 28 to 52 weeks

Series	*No. assessed**	*Cumulative incidence of candidiasis*		*Visual diagnosis and colony count on culture*					
				Definite		*Doubtful*		*None*	
		Week 36	*Week 52*	20 or more	19 to 0	20 or more	19 to 0‡	20 or more‡	19 to 0‡
B4	4	0	0	0	0	0	1	0	3
B2	8	1 (12%)†	3 (38%)†	3	0	0	0	0	5
P	23	7 (30%)†	10 (43%)†	9	0	1	1	1	11

* Nine (one B4, four B2, four P) patients with oral candidiasis seen by physician on admission or during weeks 1 to 28 have been excluded.

† Percentages based on less than 25 observations.

‡ Not classified as having oral candidiasis.

Table VI shows the rising incidence of 'oral candidiasis' in P patients changed to 800 μg beclomethasone dipropionate at 28 weeks; seven of 23 (30%) after eight weeks' treatment and 10 of 23 (43%) after 24 weeks' treatment were affected (36 weeks and 52 weeks in the trial, respectively). Three of eight B2 patients developed 'oral candidiasis' on the higher aerosol dosage, but none of the four patients who had previously received the B4 regimen blind developed 'oral candidiasis' after 28 weeks.

The total number of occasions on which the regular monthly visual examination of the throat and routine swabbing and culture for candidiasis was undertaken throughout the trial for the patients on placebo was 268 and on three (1%) of these 'oral candidiasis' was reported. For the patients on 400 μg beclomethasone dipropionate, 'oral candidiasis' was reported in 35 (10%) of 349 examinations, the corresponding proportions for patients on 800 μg being 110 (20%) of 544 examinations. (The number of examinations was highest for the 800 μg dosage because patients with an unsatisfactory response in the placebo or 400 μg series received 800 μg beclomethasone dipropionate in the second six months.) The findings at a single point in time are also of interest. Thus, considering all the patients examined in March 1973, irrespective of the date of their admission to the study, 'oral candidiasis' was present in none of 22 patients on placebo, two of 12 on 400 μg and seven of 22 on 800 μg beclomethasone dipropionate, the corresponding proportions for patients examined in June 1973 being two of 29, three of 27 and seven of 21 respectively; for September none of 21, one of 28 and six of 41, respectively; and for December none of nine, none of 20 and six of 40, respectively.

The culture results for *Candida albicans* showed the same trends. For example, considering all the cultures examined throughout the study 16 (8%) of 196 from patients on placebo at the time yielded 20 or more colonies compared with 74 (27%) of 278 patients on 400 μg beclomethasone dipropionate and 195 (42%) of 460 cultures from patients on 800 μg.

Sputum production and respiratory tract infections

The organisms isolated from sputum samples have been identified (Table VII). *Candida albicans* was isolated from sputum in only six patients (on a single occasion in

Table VII. Isolations from the sputum

Initial series	*No. assessed*	*Period of assessment and no. of possible assessments per patient*	*No. producing sputum specimens*	*No. from whom 'pathogens' were isolated*	*Organisms isolated*†																		
					Conceivably a pathogen‡									*Common commensals*									
					SA	P	KP	PA	HI	SP	EC	A	CA	SV	NS	CO	C	SE	SF	M	NH	HP	HS
B4	25	Pre-trial (3)	17	9	3	0	0	0	6	1	1	0	0	17	10	3	2	6	1	0	1	0	0
		1–28 weeks (8)	9	9	3	0	0	1	5	1	4	0	0	7	7	5	7	3	2	2	0	0	0
		29–52 weeks (6)	6	1	0	0	0	0	0	0	1	0	0	6	6	2	4	2	0	0	2	0	0
B4*	5	Pre-trial (3)	2	2	2	0	0	0	0	0	0	0	0	1	0	0	1	0	0	1	0	0	0
		1–28 weeks (8)	2	1	1	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0
		29–52 weeks (6)	0	0	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
B2	21	Pre-trial (3)	14	8	3	0	0	1	3	0	2	0	0	11	5	4	6	3	0	1	1	0	0
		1–28 weeks (8)	8	3	0	0	0	0	0	0	3	0	1	8	7	1	3	5	1	1	1	0	0
		29–52 weeks (6)	5	2	1	0	0	1	1	0	1	0	1	5	5	1	5	0	1	0	1	0	0
B2*	12	Pre-trial (3)	11	9	0	2	0	1	3	0	4	0	0	10	7	3	3	2	1	2	0	0	0
		1–28 weeks (8)	9	7	0	1	0	1	4	2	5	0	1	9	7	3	5	3	0	1	0	1	0
		29–52 weeks (6)	6	4	1	1	0	0	0	0	1	0	1	6	5	3	3	0	1	0	0	1	0
P	5	Pre-trial (3)	4	0	—	—	—	—	—	—	—	—	—	4	2	2	2	2	0	1	0	0	0
		1–28 weeks (8)	2	2	0	0	0	0	1	1	1	0	0	2	2	1	2	1	1	0	1	0	0
		29–52 weeks (6)	2	1	0	0	0	0	0	0	1	0	0	2	2	1	1	0	0	0	0	0	0
P*	27	Pre-trial (3)	15	9	1	3	0	0	4	1	4	0	0	13	6	4	1	5	0	2	0	0	1
		1–28 weeks (8)	18	13	3	5	1	1	4	1	5	0	1	17	16	11	9	7	2	1	2	0	0
		29–51 weeks (6)	12	8	3	2	0	0	1	2	3	0	1	12	12	7	4	6	2	2	0	0	0

* These patients received known 800 mg beclomethasone dipropionate from 28 weeks.

† SA = *Staph. aureus*; P = *Proteus*; KP = *Klebsiella pneumoniae*; PA = *P. aeruginosa*; HI = *Haemophilus influenzae*; SP = *Strep. pneumoniae*; EC = *E. coli*; A = *Aspergillus*; CA = *Candida albicans*; SV = *Strep. viridians*; NS = *Neisseria* sp.; CO = *Corynebacterium* spp.; C = Coliforms; SE = *Staph. epidermidis*; SF = *Strep. faecalis*; M = *Micrococcus*; NH = Non-haemolytic streptococci; HP = *H. parainfluenzae*; HS = Haemolytic streptococci.

‡ The circumstances under which these bacteria may be pathogens is not clear cut.

five and twice in one patient), despite the high incidence of 'oral candidiasis' in throat swab cultures; *Aspergillus* spp. were never seen. There was no evidence of colonization of the respiratory tract by *Pseudomonas* or *Proteus* spp. Isolations of the bacteria listed were unrelated to either the prednisone group, the aerosol dosage or to the period of treatment.

Systematic correlation has failed to show any association between the bacteria isolated and the antibiotics administered. During the first 28 weeks of the trial 14 (47%) of 30 B4 patients were prescribed antibiotics compared to 13 (39%) of 33 B2 and 16 (50%) of 32 P patients. Between 28 and 52 weeks eight (32%) of 25 B4 and 10 (48%) of 21 B2 patients who continued to receive their trial aerosol blind received antibiotics.

Sputum and throat cytology

Cytological examination of sputum and throat scrapings demonstrated desquamated cells in many patients. The numbers were unrelated to the aerosol regimen and there was no evidence to suggest gross exfoliative or atrophic change in any of the specimens examined.

DISCUSSION

Beclomethasone dipropionate administered by aerosol is now a recognized treatment for bronchial asthma. Several short-term controlled trials (Lal et al. 1972; Cameron et al. 1973; Gaddie et al. 1973; Smith et al. 1973; Hodson et al. 1974; Holst & O'Donnell 1974) have demonstrated its effectiveness in controlling asthmatic symptoms and in allowing the dosage of systemic corticosteroids to be reduced or discontinued. There are few formal studies in which systematic observations have been made over a number of months (Brompton Hospital/Medical Research Council 1974; British Thoracic and Tuberculosis Association 1975, 1976) but when drugs have to be continued for long periods, or even indefinitely, it is particularly important to observe their effectiveness and possible disadvantages in long-term studies.

The results of the first 28 weeks of this 52-week study, using beclomethasone dipropionate in corticosteroid-dependent asthmatic patients have already been reported (Brompton Hospital/Medical Research Council 1974). Data from the second part of the trial are now presented and discussed in relation to the earlier observations.

The value of the corticosteroid aerosol in chronic asthma, measured in terms of prednisone reduction, has been confirmed. During the first 28 weeks of the trial a substantial proportion of patients in the 5–9 mg and 10–15 mg groups had a good response to the 800 μg and 400 μg daily dosages. The improvement was maintained in the patients on 800 μg in both steroid groups but the 400 μg dosage was less satisfactory up to 52 weeks for the 10–15 mg group. In the small group of patients receiving 16 mg of prednisone or more the results were worse, even the 800 μg beclomethasone dipropionate, studied in five patients gave, rather disappointing results when viewed over the whole 52 weeks.

The trial was designed so that during the second half of the study patients faring badly on the allocated aerosol were changed to known beclomethasone dipropionate in high dosage (800 μg daily); the physician and the clinical assessor were, however, still unaware of the nature of the aerosol the patients had been receiving during the first 28 weeks. A striking response was seen in patients who had been receiving placebo to 28 weeks in all prednisone groups; eight of 12 in the 5–9 mg, eight of 10 in the 10–15 mg and two of five in the 16 mg or more prednisone groups were able to at least halve their initial prednisone dosage. In contrast there was a disappointing response in the patients changed from the 400 μg to 800 μg aerosol dosage. Thus, of 12 patients, only one was able to stop prednisone, although five were able to at least halve their dosage. Of five patients who went from blind B4 to known 800 μg beclomethasone dipropionate, three derived some further benefit over the second six months of the study. There was an appreciable number of patients (about 30% of the total) who did not respond to either 400 μg or 800 μg of beclomethasone dipropionate, when studied for six months or more.

Where drugs are to be used continuously over a prolonged period it is very important that their early and late side-effects are carefully appraised. Several reports showed that clinical oral candidiasis (or 'thrush') was seen in some patients, but the reported frequency has varied greatly (Brompton Hospital/Medical Research Council 1974; McAllen et al. 1974; British Thoracic and Tuberculosis Association 1975; Brown & Storey 1975; Willie et al. 1976). However, differences in methods and the diagnostic criteria adopted largely explain the different frequencies reported. These differences include the indications for and the frequency of clinical examinations of the throat, the method of swabbing, the transport of specimens and of culture examinations, the definitions adopted for laboratory and clinical diagnosis and particularly whether the results are reported as a cumulative incidence.

The present study reports the cumulative incidence of candidiasis using repeated routine assessments over a prolonged period of observation. It has also shown the lower prevalance which is found when observations are made on all patients but on a single occasion, whether or not they have symptoms. This latter is an important point, since only a minority of patients with oral candidiasis on throat inspection complain of symptoms (Brompton Hospital/Medical Research Council 1974; Willie et al. 1976).

The cumulative incidence of 'oral candidiasis' was low in patients receiving placebo aerosol and unrelated to prednisone dosage. The prevalence was high in those patients taking 400 μg beclomethasone dipropionate and higher still in patients on 800 μg, most cases appearing fairly early in the course of treatment. It is of special interest that when patients receiving placebo for 28 weeks were changed to 800 μg of beclomethasone dipropionate daily there was a sharp increase in the incidence of 'oral candidiasis', confirming the relationship between yeast infestation and the administration of corticosteroid aerosol, reported earlier (Brompton Hospital/Medical Research Council 1974). There is, however, general agreement in the literature that the presence of candidiasis is of little clinical importance and we confirm this view. Thus, in the present study, although the aerosol dosage was reduced in 10 patients owing to severe oral candidiasis, it was not necessary to stop the aerosol completely in any patient in the study.

Hodson et al. (1974) reported an increased incidence of chest infections in asthmatic patients treated with corticosteroid aerosol. In this study there was no evidence to suggest an increased incidence of infection in treated subjects. There was also no suggestion of colonization of the respiratory tract with other organisms such as *Klebsiella*, *Proteus* and *Pseudomonas* spp. So far no case of pulmonary candidiasis associated with beclomethasone dipropionate has been reported.

From the results reported here and other supporting published evidence, a reasonable programme of management for corticosteroid-dependent asthmatics is to prescribe

100 μg of beclomethasone dipropionate by aerosol four times daily and to reduce the dose of corticosteroid tablets slowly. The rate of reduction to recommend is still debated and it is possible that it was rather too rapid in the present study and that this is reflected in the rather large numbers having withdrawal symptoms (Brompton Hospital/Medical Research Council 1974). A schedule of reduction of about 2.5 mg of prednisone per week down to 10 mg and 1 mg per week thereafter would seem to be reasonable for patients who have been maintained on corticosteroid tablets for several years. A rather more rapid rate would be reasonable in the case of patients who had received regular doses of corticosteroid tablets for shorter periods. The rate, however, has to be adjusted for each individual and in some cases has to be very slow indeed.

Evidence presented here suggests that a further corticosteroid tablet sparing effect can be obtained in some individuals by increasing the dosage of beclomethasone dipropionate to 800 μg daily if the response to 400 μg is inadequate. Several studies have now confirmed that adrenal responsiveness, detected by morning cortisol measurements or by corticotrophic stimulation tests, tends to improve as corticosteroid aerosols in dosages of less than about 1000 μg are substituted for prednisone tablets (Brown et al. 1972; Cameron et al. 1973; Maberly et al. 1973). Our results (unpublished data) are in accord with this view. Adrenal suppression has, however, been recorded where the aerosol dosage is in excess of 1500 μg daily (Choo-Kang et al. 1972; Gaddie et al. 1973).

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When the bronchodilator alone is inadequate, what next?

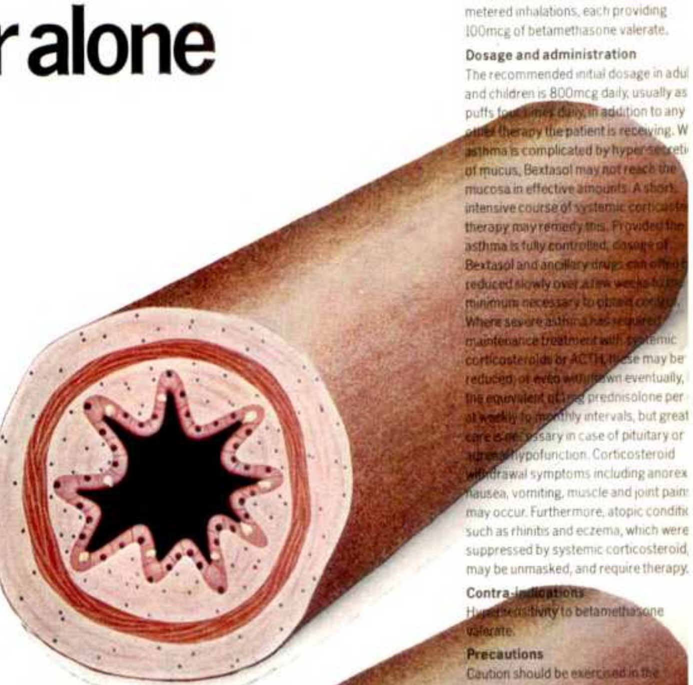
In controlling chronic asthma, the bronchodilator is usually the first line of attack. Often it will be the only treatment required.

In many cases, however, bronchodilators need to be given continuously and even then a number of patients will not be controlled satisfactorily—probably because the asthma is complicated by inflammation which bronchodilators will not control.

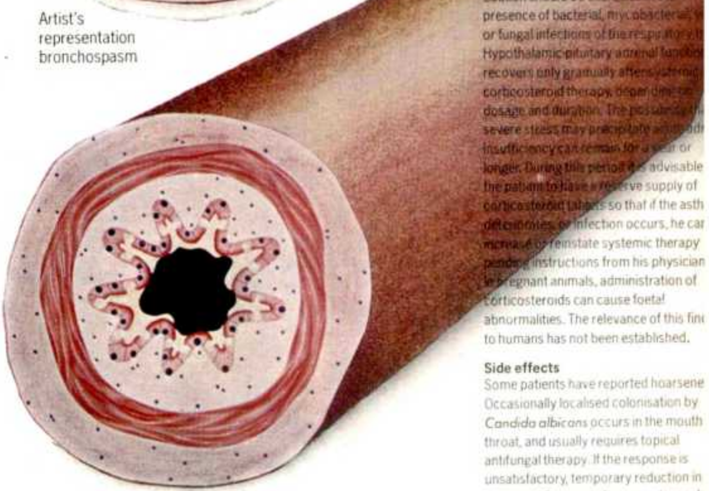
So when a second line of attack is required, Bextasol effectively controls the inflammatory process within the lungs and provides ideal prophylaxis of both intrinsic and extrinsic asthma. It offers steroid control without systemic side effects and usually produces a significant improvement in lung function.

In addition, no adverse effects on lung tissue have been reported after five years' clinical experience of inhaled steroid therapy.

In short, Bextasol inhaler allows the asthmatic to breathe and to live life to the full.



Artist's representation bronchospasm



Bronchospasm complicated by mucosal oedema and hypersecretion of mucus.

the clear decision

(betamethasone valerate)

Prescribing information

Presentation

A pressurised aerosol containing a suspension of betamethasone valerate with propellants which supplies 200 metered inhalations, each providing 100mcg of betamethasone valerate.

Dosage and administration

The recommended initial dosage in adul and children is 800mcg daily, usually as puffs four times daily, in addition to any other therapy the patient is receiving. W asthma is complicated by hyper-secreti of mucus, Bextasol may not reach the mucosa in effective amounts. A short intensive course of systemic corticoste therapy may remedy this. Provided the asthma is fully controlled, dosage of Bextasol and ancillary drugs can often b reduced slowly over a few weeks to the minimum necessary to obtain control. Where severe asthma has required maintenance treatment with systemic corticosteroids or ACTH, these may be reduced, or even withdrawn eventually, the equivalent of 1mg prednisolone per at weekly to monthly intervals, but great care is necessary in case of pituitary or adrenal hypofunction. Corticosteroid withdrawal symptoms including anorex nausea, vomiting, muscle and joint pain may occur. Furthermore, atopic conditi such as rhinitis and eczema, which were suppressed by systemic corticosteroid, may be unmasked, and require therapy.

Contra-indications

Hypersensitivity to betamethasone valerate.

Precautions

Caution should be exercised in the presence of bacterial, mycobacterial, v or fungal infections of the respiratory t Hypothalamic-pituitary adrenal functio recovers only gradually after systemic corticosteroid therapy, depending on the dosage and duration. The possibility th severe stress may precipitate acute adr insufficiency can remain for a year or longer. During this period it is advisable the patient to have a reserve supply of corticosteroid tablets so that if the asth deteriorates or infection occurs, he car increase or reinstate systemic therapy pending instructions from his physician. In pregnant animals, administration of corticosteroids can cause foetal abnormalities. The relevance of this fin to humans has not been established.

Side effects

Some patients have reported hoarsene Occasionally localised colonisation by *Candida albicans* occurs in the mouth throat, and usually requires topical antifungal therapy. If the response is unsatisfactory, temporary reduction in dosage of Bextasol often speeds resol

See Data Sheet for complete informati

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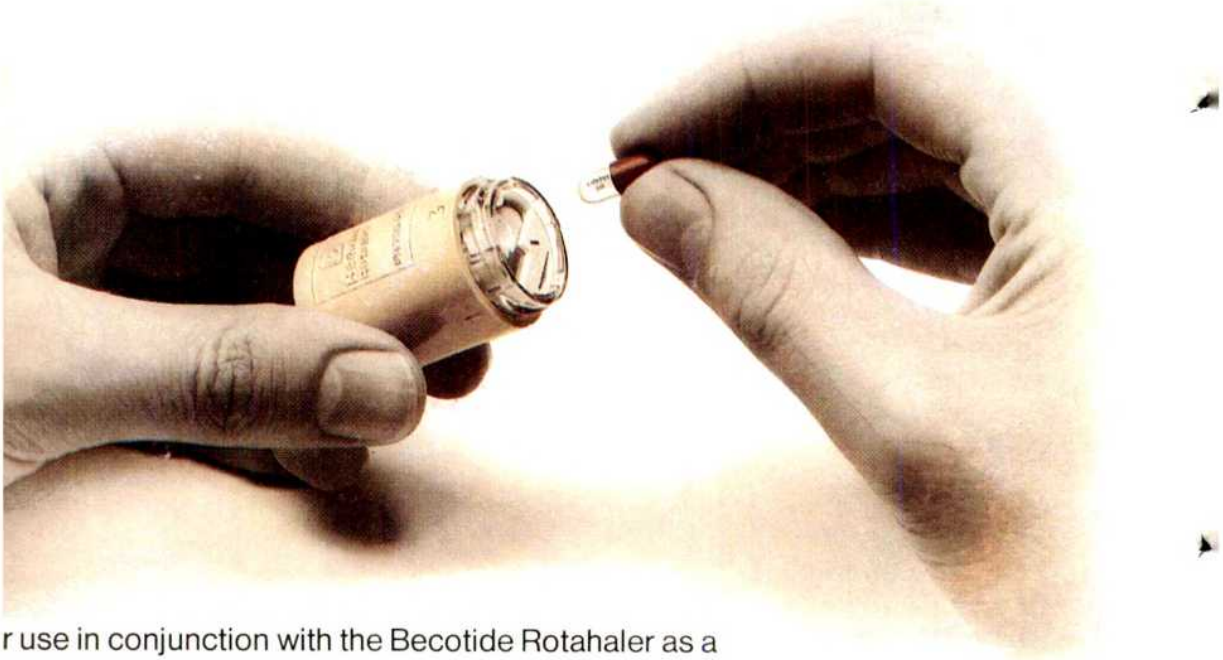

r use in conjunction with the Becotide Rotahaler as a
›ath-actuated alternative to Becotide Inhaler

A GREATER DEGREE OF CERTAINTY – A

:OTIDE ROTACAPS PRESCRIBING INFORMATION

:ENTATION
tide Rotacaps, an alternative inhalation form of beclomethasone dipropionate to
tide Inhaler, are especially valuable for treating patients who are unable to use
urised inhalers effectively or who might use them incorrectly.
tide Rotacaps contain a mixture of microfine beclomethasone dipropionate BP
arger particle lactose in buff or chocolate-brown/colourless hard gelatine
dges. Each Becotide Rotacap contains 100 micrograms (buff) or 200 micrograms
olate-brown) of beclomethasone dipropionate BP and is marked Becotide 100
cotide 200. The contents of a Rotacap are inhaled using a specially developed
e called a Rotahaler which cuts the cartridge into two halves that rotate and
se the drug when the patient inhales. This breath actuation is very sensitive and
drug is fully available even at the lowest inspiratory rates.

:ATIONS
ide Rotacaps are indicated for a wide range of patients with bronchial asthma.
patients include: those whose asthma is becoming worse and the relief
ded by bronchodilators is less effective; those who are inadequately controlled
dium cromoglycate in addition to bronchodilators; those with severe asthma
are dependent on systemic corticosteroids, or adrenocorticotrophic hormone
H) or its synthetic equivalent.
ide Rotacaps are particularly important for managing severe asthma in children

DOSAGE AND ADMINISTRATION
Becotide Rotacaps are for inhalation use only, using a Becotide Rotahaler. For optimum results Becotide Rotacaps should be used regularly.
Adults: One 200 micrograms Rotacap, three or four times a day is the usual maintenance dose.
Children: One 100 micrograms Rotacap two, three or four times a day, according to the response.

CONTRA-INDICATIONS
No specific contra-indications to Becotide Rotacaps are known, but special care is necessary in patients with active or quiescent pulmonary tuberculosis.

PRECAUTIONS
Patients should be instructed in the proper use of the Rotahaler to ensure that the drug reaches the target areas within the lungs. They should also be made aware that Becotide Rotacaps have to be used regularly for optimum benefit.
The maximum daily intake of beclomethasone dipropionate should not exceed 1mg; significant reduction of plasma cortisol levels has been reported in patients who received twice this amount.
Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.
If there is no response to therapy within a week in patients previously not treated with systemic steroids or ACTH then consideration should be given to the probability that excessive mucus in the bronchi has prevented the drug from penetrating to its site of

nhaled steroid therapy of asthm

ROTACAPS*

e of patients with chronic asthma

Becotide Inhaler is well established for the treatment of chronic asthma where inflammatory changes within the lungs reduce the response to bronchodilators; and for many previously steroid-dependent patients in eliminating or greatly reducing their need for systemic steroids, particularly severely asthmatic children who would be at risk from systemic side effects such as stunting of growth.

However, there are patients who do not obtain maximum effectiveness from Becotide Inhaler, and the Rotacaps/Rotahaler System has been developed with them in mind providing –

Breath-actuated control – for children, and those elderly or arthritic patients who may find it easier and more reliable.

Avoidance of faulty inhaler technique – for those patients who cannot co-ordinate the action of breathing in with the activation of a pressurised aerosol.

A better guarantee of effectiveness – for patients in whom Becotide Inhaler has not provided the anticipated benefit probably because of inadequate delivery of drug.

Appropriate routine prophylaxis – a way of helping to ensure that Becotide is used routinely by those patients who might misunderstand its role.

ETTER GUARANTEE OF EFFECTIVENESS

apparent ineffectiveness before the trial of a short course of systemic steroid in relatively high dosage has been given to control secretion of mucus and other inflammatory changes in the lungs.
When transferring patients to Becotide Rotacaps from systemic steroids, please refer to the detailed procedure described in the Data Sheet.

SIDE EFFECTS
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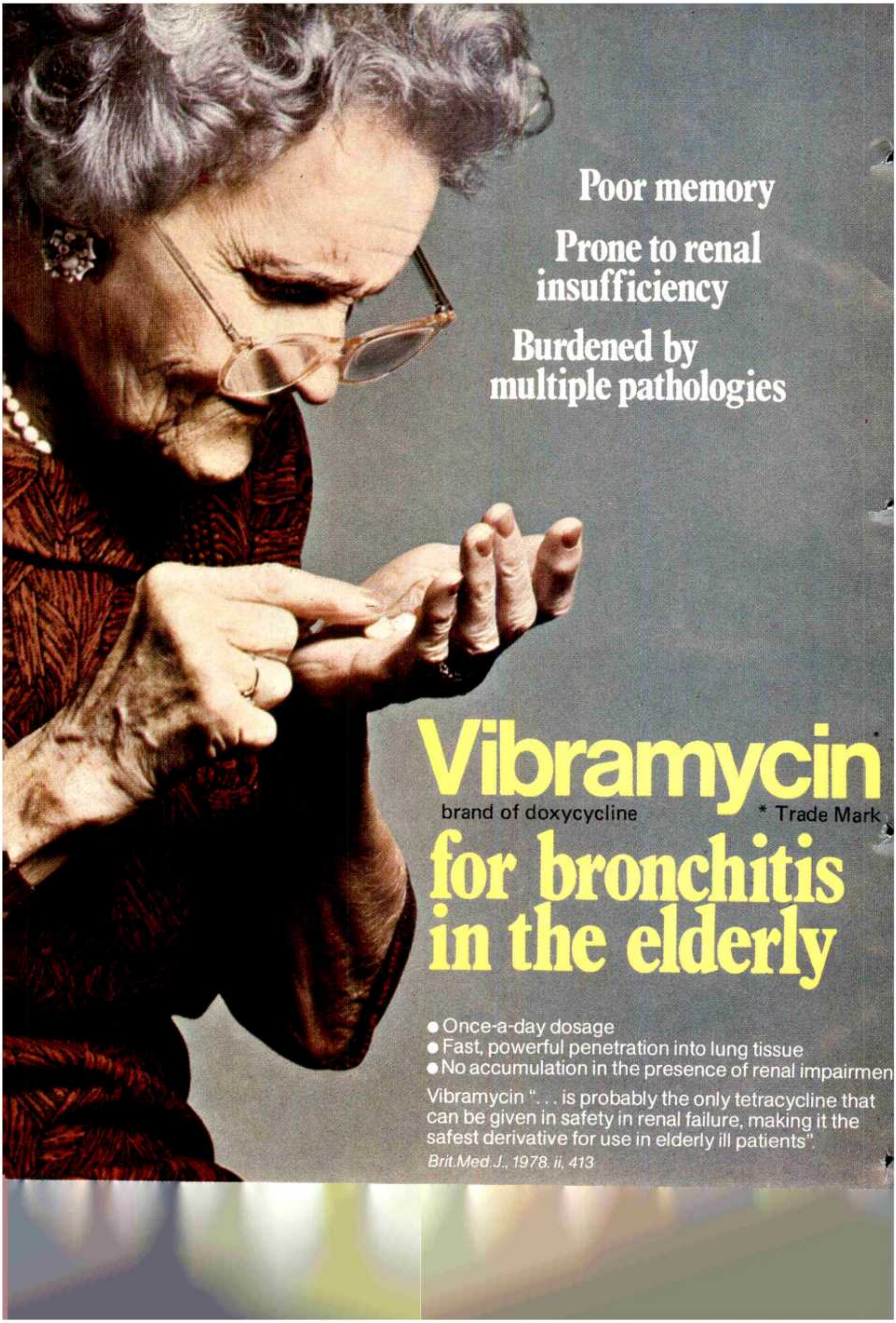

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LARGE PLEURAL EFFUSIONS IN RHEUMATOID ARTHRITIS

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An association of lung disease and rheumatoid arthritis was noted as long ago as 1860 by H. W. Fuller in his book on rheumatic conditions and by J. M. Charcot in his lecture to the New Sydenham Society in 1881, where he mentioned pleurisy and empyema. A. E. Garrod (1890) discussed visceral lesions in rheumatoid arthritis, concluding that they were due to intercurrent illness. In 1897, G. E. Still described three juveniles with rheumatoid disease who had pleural effusions at autopsy, and he thought it perhaps peculiar to the juvenile form of the disease.

Pleural effusions in association with rheumatoid arthritis have been described many times (Ellman & Ball 1948; Gruenwald 1948; Raven et al. 1948; Ellman & Cudkowicz 1954; Aronoff et al. 1955; Emerson 1956; Sinclair & Cruickshank 1956; Horler & Thompson 1959; Flatley 1959; Lee 1959; Cudkowitz et al. 1961; Ward 1961; Caplan et al. 1962; Carr & Mayne 1962; Schools & Mikkelson 1962; Talbot & Calkins 1964; Brannan et al. 1964; Stack & Grant 1965; Lassiter et al. 1965; Hindle & Yates 1965; Davies 1966; Carmichael & Golding 1967; Rubin et al. 1967; Walker & Wright 1967; Campbell & Ferrington 1968; Scadding 1969; Lillington et al. 1971; Kay & Banik 1977). Empyema is also associated with rheumatoid arthritis (Kellgren et al. 1958; Jones & Blodgett 1971; Huskisson & Hart 1972; Dieppe 1975), though Blau (1971) disputes this. Effusions usually occur in middle-aged men; they are rarely seen in the under 40 age group (Lillington et al. 1971). The effusion is almost always an exudate, often clear yellowish-green fluid, but sometimes appears purulent though sterile on culture (Hindle & Yates 1965; Davies 1966). Chyliform fluid is sometimes seen (Davies 1966; Lillington et al. 1971) and the cholesterol and other lipid levels are shown to be raised in those cases (Carr & Mayne 1962; Bower 1968).

The size of the effusion is small very often, but Walker and Wright (1967) suggest effusions usually fill one-third to half of the hemithorax and large effusions are described (Emerson 1956; Lee 1959; Ward 1961; Stack & Grant 1965; Campbell & Ferrington 1968). They may be found on either side of the chest or bilaterally. They are notable for being persistent and recurrent (Lee 1959; Flatley 1959; Carr & Mayne 1962).

Subcutaneous nodules were first described histologically by Collins (1937); pleural nodules, with similar histology, were described by Bennett et al. (1940). Raven et al. (1948) described a single case with bilateral small effusions and pleural nodules seen at autopsy. Pleural nodules have since been described on many occasions (Flatley 1959; Cudkowitz et al. 1961; Schools & Mikkelson 1962; Hindle & Yates 1965; Rubin et al. 1967; Jones 1971). Hindle and Yates (1965) discuss the ease with which pleural nodules may be seen on tomography of the chest.

Bronchopleural fistula development arising from the necrotic pleural nodules is well described and frequently fatal (Cudkowitz et al. 1961; Davies 1966; Rubin et al. 1967; Jones & Blodgett 1971) and Davies (1966) suggests how the degenerating nodules exude material into the pleural space, accounting for the type of fluid often found, and breaking back sometimes into the bronchial tree to cause the fistula.

A pleural biopsy to determine the aetiology of an effusion was first used in tuberculosis by Sutcliffe et al. (1954); Rubin (1955) and Heller et al. (1956) describe its use in rheumatoid arthritis effusions. The importance of biopsy is demonstrable in the work of many authors (Lee 1959; Schools & Mikkelson 1962; Jones & Blodgett 1971), but especially in that of Campbell and Ferrington (1968), who stressed this importance, describing cases where repeated biopsies eventually gave material diagnostic of rheumatoid arthritis. Others mention material removed at thoracotomy (Flatley 1959; Hindle & Yates 1965; Lillington et al. 1971). Ward (1961) described cases with negative biopsies.

That pulmonary lesions are associated with rheumatoid arthritis was disputed; the Empire Rheumatism Council Report (1950) found only 7% of systemic problems, but they were interviewing patients quite near the onset of disease. Aronoff et al. (1955), in a large series, found little association. But Sinclair and Cruickshank (1956), Cruikshank (1957) and Talbot and Calkins (1964) found strong association.

We saw two cases of large pleural effusion in association with rheumatoid arthritis quite by chance in the first three months of 1977, on a general medical firm. A third case, more long-standing, was then referred to us and is described first.

Case Reports

Case 1

A 54-year-old woman was admitted in May 1976 with shortness of breath, cough and right chest pain. She had had rheumatoid arthritis for 25 years and had had a right pleural effusion tapped 20 years before.

On this occasion she had gross changes of rheumatoid arthritis with nodules and deformity of wrists, hands, knees and feet. She had had all toes amputated 10 years previously. She was febrile with signs of a right pleural effusion, and a chest radiograph showed bilateral pleural effusions (Fig. 1), more marked on the right. Other investigations revealed a haemoglobin of 10.3 g/100 ml, WBC 12 000/mm^3, ESR 65 mm/hour (Westergren). Rose Waaler and Latex test were positive and anti-nuclear factor negative.

Right and left pleural taps revealed viscid green-coloured fluid, which was sterile and contained no sugar. She remained febrile with a raised white count, and was treated with cephredine and cloxacillin. There was no improvement; the pleural effusions increased in size again and the ESR was 93 mm/hour. The serum albumin was low at 33 g/litre. A further chest radiograph showed hydropneumothorax after each of the aspirations.

She was transferred to a thoracic surgical department and further aspirations revealed sterile fluid with no sugar detectable and protein content of 48 g/litre on the right, 28 g/litre on the left with cholesterol crystals. She was discharged with small bilateral effusions which persisted over the next eight months.

She was readmitted in January 1977 with severe breathlessness and a fever. Bilateral pleural effusions were again found. The left was blood-stained but the right aspiration revealed pus. This was sterile and she was given penicillin and gentamicin and improved. *Pneumococcus* was cultured from the sputum. Rheumatoid factor was positive to a titre of 1:2560 and the ESR was 122 mm/hour. When seen at out-patients in April 1977, small bilateral effusions were still present and the ESR was 64 mm/hour.

She was readmitted again in August 1977 with bilateral pleural effusions; she had further taps and because of persistent bilateral pleurisy we inserted 25 mg triamcinolone into each pleural space. In October she was seen again, still with small effusions, but no pleurisy.

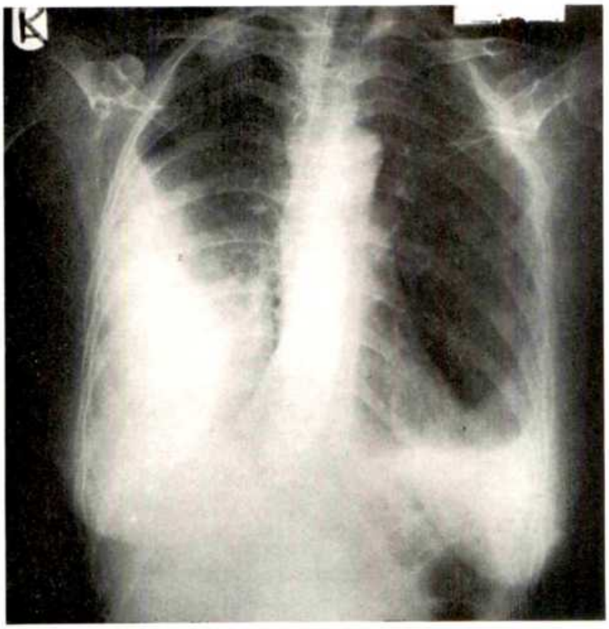

Fig. 1. Case 1. Large pleural effusion of the right with some collapse of the lung and a smaller effusion on the left

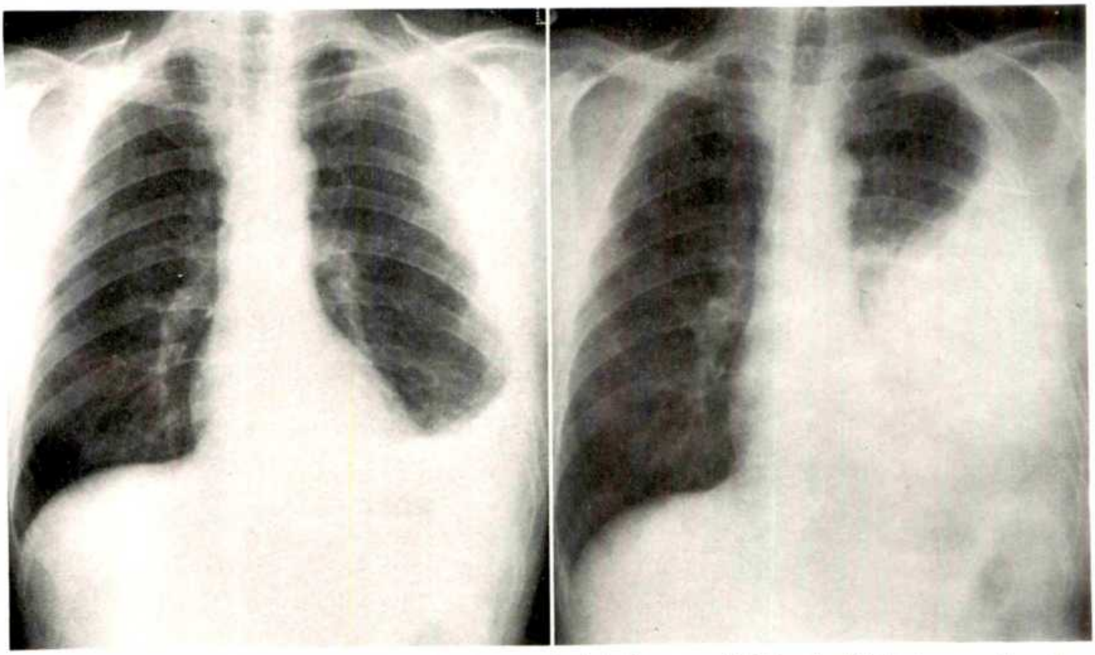

Fig. 2. Case 2. *Left,* Small pleural effusion at the left base on 15 March. *Right,* Large pleural effusion on the left on 28 March

Case 2

A man aged 48 presented in February 1977 having had rheumatoid arthritis for two months. His right shoulder, hands and knees were especially affected. He had marked morning stiffness. There were no nodules. Initial examination was otherwise normal. His ESR was 42 mm/hour and rheumatoid factor was negative; antinuclear factor was weakly positive. He initially had an eosinophilia. He was admitted in March because the joints were worsening; an initial chest radiograph was clear.

Within a few days of his admission a left pleural effusion appeared, very small at first, but rapidly enlarging (Fig. 2). He had a swinging pyrexia. At this time his ESR was over 100 mm/hour and his Latex test positive. The effusion was tapped; straw-coloured fluid was examined and was sterile; protein content was 50 g/litre and sugar <1 mmol/litre. Pus cells were present. He was treated with antibiotics but the fever remained until all the fluid was aspirated. Pleural biopsy showed acutely inflamed granulation tissue. No acid-fast bacilli was found in the fluid or biopsy. Rectal biopsy was normal. The serum albumin was normal.

He was treated with aspirin and indomethacin and clinically his joints improved. His ESR remains >100 mm/hour. The effusion remained clear, when he was seen in September 1977, though his arthritis was still active.

Case 3

A man aged 65 was admitted in April 1977 with a one-month history of increasing shortness of breath and six years of rheumatoid arthritis. He was found to have bilateral pleural effusions left greater than right (Fig. 3) and he had gross changes of rheumatoid arthritis in the hands, knees, and feet and had rheumatoid nodules. He also had a raised venous pressure and sacral and ankle oedema on admission; these responded to diuretics but the effusions remained. Left pleural tap revealed cloudy, straw-coloured fluid containing 39 g/litre of protein and 1 mmol/litre of sugar.

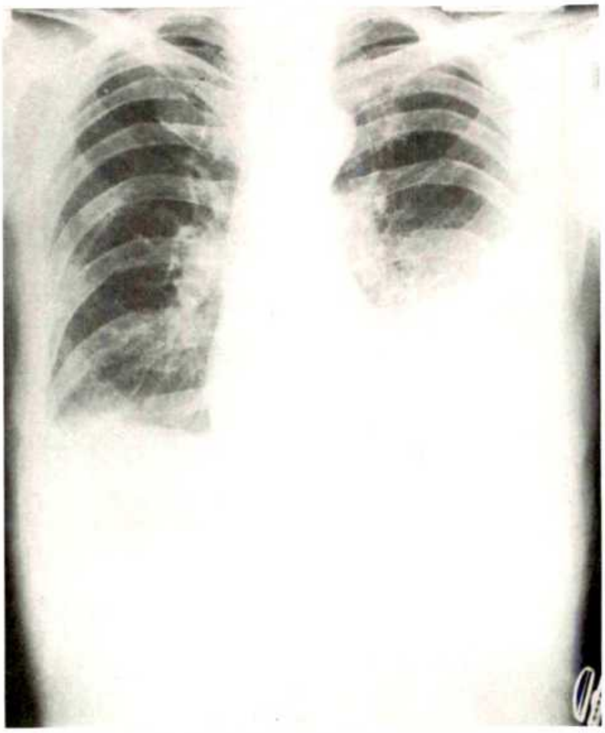

Fig. 3. Case 3. Moderate pleural effusion on the left with small effusion on the right

His rheumatoid factor was positive to a titre of 1/10 240 as it had been a year before. The ESR was over 100 mm/hour and his serum albumin was low at 26 g/litre. Left pleural biopsy was negative, rectal biopsy was also negative. Antinuclear factor was weakly positive. He was treated with prednisolone in large dosage for two weeks with relief of pain but no clinical improvement. His ESR remained over 100 mm/hour at dischage. The pleural effusions were almost clear.

DISCUSSION

Our cases posed us difficulties in diagnosis and we admit to feeling that other causes play a part in the development of these effusions. Pleural biopsy was unhelpful in two cases, but we took only single samples.

Further aids to diagnosis, less invasive and more reliable than pleural biopsy, have been sought in the pleural fluid examination. Typical 'rheumatoid arthritis cells' have been seen by Carmichael and Golding (1967) and Jones and Blodgett (1971), but these are difficult to identify.

We found the low sugar content of the effusion most helpful. Carr and Power (1960) and Carr and Mayne (1962) described this low sugar content of the pleural fluid in rheumatoid arthritis. This has since been often demonstrated (Schools & Mikkelsen 1962; Walker 1967; Campbell & Ferrington 1968; Scadding 1969; Jones & Blodgett 1971; Lillington et al. 1971). Lillington et al. (1971) suggested that with a normal sugar level one might be justified in suspecting disseminated lupus erythematosus rather than rheumatoid arthritis.

Rheumatoid factor has been found to be positive in the pleural fluid, usually to a greater degree than in the blood (Lee 1959; Schools & Mikkelsen 1962; Walker & Wright 1967; Jones & Blodgett 1971; Lillington et al. 1971) though this can occur in other cases of effusion due to such things as tuberculosis and carcinoma (Levine 1968).

Leaving the fluid itself for a moment, rheumatoid factor (or its equivalent at the time) has been noted to be especially high in patients with rheumatoid effusions (Ward 1961; Caplan et al. 1962; Hindle & Yates 1965; Walker & Wright 1967), though Walker and Wright (1967) suggest that there was no association of level of rheumatoid factor in the blood and the presence of effusion. Rheumatoid factor in the blood has been discussed in relation to other pulmonary manifestations, notably Caplan et al. (1962) describing 269 coalworkers with positive rheumatoid factor in 88%; while 64% had clinical features of rheumatoid arthritis, eight of these had pleural effusions and seven had positive rheumatoid factor. Tomasi et al. (1962), not mentioning effusions, describe more pulmonary lesions in those with higher rheumatoid factors.

The simple protein content of the pleural fluid ranges from 3 to 7.6 g/100 ml in most cases (Carr & Mayne 1962; Schools & Mikkelson 1962; Walker & Wright 1967; Campbell & Ferrington 1968; Jones & Blodgett 1971); though Ellman and Cudkowicz (1954) describe cases, one of whom had a transudate.

The white cell count of the fluid usually shows an excess of lymphocytes, but occasionally as many as 90% polymorphonuclear leucocytes have been described on sterile fluid without antibiotic history (Schools & Mikkelson 1962; Davies 1966; Carmichael & Golding 1967; Walker & Wright 1967; Campbell & Ferrington 1968). Raised LDH levels have also been noted in the pleural fluid (Campbell & Ferrington 1968; Jones & Blodgett 1971; Lillington et al. 1971) but this happens in many other conditions too (Lillington et al. 1971).

The association of rheumatoid arthritis and empyema already mentioned brings up the association of rheumatoid arthritis and infection aetiologically in either direction. Cobb et al. (1953) noticed an increased incidence of infections causing death in a series of 583 rheumatoid arthritis sufferers, 130 of whom had died. Kellgren et al. (1958) described a variety of infections arising in rheumatoid arthritis patients. Walker (1967) and Kay (1967) also thoroughly describe the increased incidence of bronchitis, pneumonia and especially bronchiectasis in rheumatoid arthritis patients. Baum (1971) and Huskisson and Hart (1972) deal with this topic and with Walker and Wright (1967) can show no influence of corticosteroid treatment on the infection here.

Infections could possibly cause the arthritis; the tendency to increased infection can certainly antedate the onset of arthritis (Kay 1967; Walker 1967), as can pleural effusion and other pulmonary lesions (Ward 1961; Brannan et al. 1964; Davies 1966).

The other pulmonary lesions consist mainly of dry pleurisy and parenchymal lung disease of patchy or diffuse form, all more common at the lung bases (Ellman & Ball 1948; Raven et al. 1948; Caplan 1953; Rubin 1955; Horler & Thompson 1959; Cudkowitz et al. 1961; Ward 1961; Doctor & Snider 1962; Brannan et al. 1964; Stack & Grant 1965) and a case of pulmonary hypertension (Kay & Banik 1977).

CONCLUSION

Our three cases illustrate many of the classical features of pleural effusion complicating rheumatoid arthritis. Effusions were bilateral in all cases though there was an especially large effusion on one side in all cases as well. The effusions contained low or undetectable sugar contents. Two single pleural biopsies were carried out, which were unhelpful. The patients had severe disease, though in Case 2 this had been of only short duration; the level of rheumatoid factor was high in each case. As with so many syndromes the extra large size of these effusions probably has many causes. Not only is the 'rheumatoid disease' (Ellman & Ball 1948; Rubin 1955) tending to cause the effusion, but infection may have played a part in Cases 1 and 2 though no organism was isolated from the fluid in either case, and a low serum albumin may have increased the tendency to effusion in Cases 1 and 3, while in Case 3 heart failure could have been sufficiently severe to contribute. Triamcinalone was inserted into the pleural spaces of Case 1 with reduction in pleurisy but no definite effect on effusion.

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TUBERCULOSIS IN RENAL TRANSPLANT RECIPIENTS

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Summary

Of more than 400 patients who received renal transplants in Cambridge, five subsequently developed tuberculosis. All had pulmonary involvement. Radiological abnormalities included miliary opacities, bilateral lower zone shadowing or typical upper zone shadowing with cavitation. Lung biopsy was required for diagnosis in two cases. Three patients recovered after treatment with antituberculosis drugs and none has relapsed. One died during chemotherapy despite drug-susceptible organisms. The problems encountered during chemotherapy are discussed.

INTRODUCTION

Although pulmonary infection is common amongst recipients of renal transplants, tuberculosis has been described only infrequently. We report five cases of pulmonary tuberculosis in patients who have received renal transplants and discuss the problems of diagnosis, treatment and prevention.

Patients

Five patients who received cadaver renal transplants in Cambridge between 1966 and 1977 are known to have developed tuberculosis and details of their history are given in Table I.

Four of the patients were white and born in the United Kingdom and one (Case 4) was an Asian immigrant. No patient had any personal or family history of tuberculosis nor any known contact with the disease. Tuberculin testing was not carried out preoperatively and none of the patients had received BCG. Only one patient (Case 2) had an abnormal pretransplantation chest radiograph and this showed bilateral apical pleural thickening which had been present and unchanged for at least two years.

Two patients died with tuberculosis. One (Case 2) developed the disease after renal transplant nephrectomy and return to haemodialysis. She improved initially on antituberculosis treatment (organisms beng susceptible to the drugs used) but miliary shadowing persisted on her chest radiograph. After three months of antituberculosis treatment a fluctuant swelling developed on her left thigh from which purulent material was aspirated. No tubercle bacilli, bacteria or fungi were isolated. At autopsy numerous tubercles were found in both lungs and there was a well-defined caseous focus near the apex of the right upper lobe in communication with a bronchus. Tubercles were also found on the peritoneum and in both fallopian tubes. Tubercle bacilli could not be isolated from any of these sites, or from the contents of the abscess in the leg.

The management of the other patient who died (Case 5) was largely undertaken at another

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Table I.

Patient	*Age at transplant*	*Sex*	*Course after transplantation*	*Time from transplant**	*Symptoms**	*Immuno-suppressant**	*Blood urea** (mmol /litre)
1	48	F	Rejection episode at 28 months	37 months	Productive cough Breathless on exertion Anorexia Weight loss Fever Punched-out ulcer in popliteal fossa	Prednisolone 15 mg daily daily Azathioprine 75 mg daily	16
2	46	F	Graft rejection at 4 months Transplant nephrectomy at 6 months	8 months	Malaise Breathlessness	Prednisolone 2.5 mg daily	10.8
3	20	M	Uneventful	76 months	None Admitted to cough on direct questioning	Prednisolone 8 mg daily Azathioprine 200 mg daily	7.5
4	38	M	Persistent tachycardia Weight loss Indolent abscess at shunt site Diabetes mellitus at 4 months	10 months	None	Prednisolone 30 mg daily Azathioprine 125 mg daily	4.0
5	36	M	Diabetes mellitus Pulmonary arterial hypertension Recurrent chest infections	7 years	Not known	Prednisolone Azathioprine	—

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* At time of diagnosis of tuberculosis.

◄Patient details

*Radiological appearances**	*Specimens examined for tubercle bacilli**	*Treatment*	*Duration of treatment*	*Outcome*
Ill-defined shadowing both lower lobes	Sputum, urine, ulcer surface: all smear positive	Rifampicin 450 mg daily Isoniazid 200 mg daily	18 months	Well one year after completing treatment
Miliary shadowing Ill-defined peripheral opacity, left second interspace Bilateral apical pleural thickening	Drill lung biopsy: smear positive Sputum: culture positive Bone marrow: smear and culture negative	Rifampicin 450 mg daily Isoniazid 200 mg daily Streptomycin 0.75 g i.m. twice weekly two hours before haemodialysis	6 months	Died while receiving treatment
Right upper lobe cavitation and shadowing	Sputum: smear and culture positive	Rifampicin 600 mg daily Ethambutol 25 mg/kg daily Isoniazid 300 mg daily	2 months	Well two years after completing treatment
		Isoniazid 300 mg daily Ethambutol 15 mg/kg daily	Further 15 months	
		Isoniazid 300 mg daily	Further 18 months	
Nodular shadows both upper and middle zones Cavity left upper zone	Needle lung biopsy: culture positive Urine: smear and culture positive	Rifampicin 450 mg daily Ethambutol 15 mg/kg daily Isoniazid 300 mg daily	4 weeks	Well two years after after completing treatment
		Streptomycin 0.5 g daily Pyrazinamide 1.5 g daily Rifampicin 450 mg daily Isoniazid 300 mg daily	4 weeks	
		Rifampicin 450 mg daily Isoniazid 300 mg daily	Further 18 months	
Cardiomegaly Pulmonary oedema	Post-mortem culture of pleura positive	None		Died

hospital and it has not been possible to obtain full details of his progress after transplantation or of his final illness. At autopsy tubercles were found in the lungs and on the pleural and mesentery. Histologically tubercles were seen in many organs and *Mycobacterium tuberculosis* was cultured from the pleura.

DISCUSSION

Despite the well recognized predisposition of renal transplant recipients to pulmonary infection, few cases with tuberculosis have been reported. Hill et al. (1967) recovered *M. tuberculosis* at autopsy in two of 60 patients who had died 25 days or more after transplantation, and a later report from the same centre (Neff & Hudgel 1973) stated that only three cases of active tuberculosis had occurred in over 400 renal transplant recipients. Stake and Flatmark (1976) briefly mention a single case of pulmonary tuberculosis in a review of pulmonary complications after more than 77 renal transplants. A further case has recently been reported by Al Batata (1977). Likewise infection with atypical mycobacteria has been reported in only three patients after renal transplantation (Graybill et al. 1974; Fraser et al. 1975). Over 400 patients received renal transplants in Cambridge between 1966 and mid 1977, and five are known to have subsequently developed tuberculosis. This incidence is rather higher than that reported elsewhere but the reasons for this are unknown. None of our patients gave a history of previous tuberculosis or of recent exposure to the disease. In only one case did review of the previous chest radiographs reveal changes which might have been due to previous tuberculous infection. There was no evidence of tuberculosis amongst staff of the renal unit during this period.

Pathogenesis

It is generally accepted that pulmonary tuberculosis in the normal adult usually represents reactivation of previously dormant infection (Stead 1967), although primary infection may occur at any age. Tuberculosis in our patients and in those discussed in the literature had the radiological appearance and clinical course either of typical reactivation with predominantly upper lobe disease, often with cavitation or, less often, of widely disseminated disease involving other organs as well as the lung. Such wide dissemination cannot be presumed to indicate recent primary infection, however, especially when localization may be impaired by one or more factors present after organ transplantation. In one or our patients (Case 2) dissemination seemed to have followed rupture of a pulmonary lesion into a bronchus and possibly into a pulmonary vessel. In one report (Lakshminarayan & Sahn 1973) it was suggested that infection had been introduced in the donor kidney.

The increased risk of tuberculosis in recipients of renal transplants may well be related to therapy with corticosteroids or azothioprine but other factors must be considered. The role of chronic renal failure in altering susceptibility to tuberculosis is unknown. There is some laboratory evidence that serum bactericidal activity and lymphocyte transformation may be impaired in renal failure (Montgomerie et al. 1972; Nakhla & Goggin 1973). Two of our five patients had good renal function at the time that tuberculosis was recognized, however. Pradhan et al. (1974) recorded five cases of active tuberculosis among 136 patients who had received regular haemodialysis for an average period of 1.4 years, and they suggested that there is an increased risk of contracting tuberculosis during chronic haemodialysis.

The role of corticosteroid therapy in precipitating reactivation of previously quiescent tuberculosis has recently been reviewed (Lakshminarayan & Sahn 1976). After examination of their own data and a review of published reports these authors concluded that they were unable to prove or disprove the contention that corticosteroids do reactivate latent tuberculosis. Many of the patients who had developed tuberculosis had received corticosteroids for treatment of conditions which themselves impair host defence mechanisms. All of our patients were receiving corticosteroids. Two (Cases 3 and 5) had been taking stable low doses (of the order of 10 mg daily of prednisolone) for over six years at the time of their tuberculous illnesses and the other three had received high doses of prednisolone or related drugs within one year before detection of tuberculosis, either during the post-transplantation period or for treatment of threatened rejection. Fungal and nocardial infections after organ transplantation are frequently related to prior episodes of rejection or to their treatment (Bach et al. 1973) but we have no evidence either for or against such an association with the development of tuberculosis.

Similar difficulties complicate assessment of the role of azothioprine in reactivating tuberculosis. Experience of non-corticosteroid immunity-suppressing agents has been mainly in the treatment of malignant disease and an increased incidence of tuberculosis has been recorded in a variety of malignant conditions (Kaplan et al. 1974). Likewise in the lymphoproliferative disorders tuberculosis may occur more commonly than in other groups of comparable ages. It tends to occur especially after the start of drug therapy for neoplasms, when it is much more severe with higher mortality, particularly so if they are also receiving corticosteroids (Kaplan et al. 1974). Further risk factors have been identified in renal transplant recipients who develop infections (Eickhoff et al. 1972). Leucopenia and moderate or severe renal failure are significantly associated with fatal infections, and hyperglycaemia for more than two weeks or high dosage of prednisone for at least two weeks is even more hazardous in this respect. There is an increased risk of infection in patients over 40. Both our patients who died were over 40, but were not much older than two of those who survived. One was diabetic and the other had renal failure and leucopenia.

Clinical features and diagnosis

The clinical and radiological features of tuberculosis in our five patients differed widely. Only one (Case 1) complained of cough and only two were breathless at the time of diagnosis—one (Case 1) with bilateral lower zone tuberculous pneumonia and the other (Case 2) with miliary disease. There was evidence of extrapulmonary spread in four patients. One (Case 1) had a tuberculous skin ulcer, one (Case 4) had *M. tuberculosis* isolated from his urine and both those who died had widely disseminated disease at autopsy.

In the four patients in whom the diagnosis of tuberculosis was made in life, suspicion was raised by an abnormal chest radiograph. Two had typical appearances of cavitated upper lobe disease, one had bilateral lower lobe pneumonic changes and miliary opacities were seen in the radiograph of one patient. The fifth patient had changes compatible with left ventricular failure on chest radiograph but no evidence of tuberculosis.

Confirmation of the diagnosis was not always easy even when the possibility of tuberculosis had been recognized. Acid-alcohol fast organisms were seen in sputum of only two of our patients. Recourse was made to lung biopsy in two others who were unable to raise sputum. High speed air-drill biopsy on one patient (Case 2) yielded lung tissue containing caseating lesions in which a single acid-fast organism was seen after prolonged search. Percutaneous aspiration needle biopsy of the upper lobe lesion in Case 4 yielded material from which no histological diagnosis could be made but which subsequently yielded *M. tuberculosis* on culture. In all the patients diagnosed in life the infecting organism was *M. tuberculosis* var. *hominis* and was fully susceptible to the standard antituberculosis drugs.

Problems in management

Treatment of tuberculosis in renal transplant recipients poses three problems. First, excretion of three of the commonly used antituberculous drugs—isoniazid, streptomycin and ethambutol—is dependent upon adequate renal function and accumulation may occur with risk of toxicity if renal failure is present. Secondly, rifampicin has been shown to induce hepatic enzymes (Edwards et al. 1974) and may thereby interfere with the action of prednisolone. Thirdly, little information is available on the necessary duration of chemotherapy in the presence of abnormal host defences.

Antituberculosis chemotherapy was successful and without adverse effects in three of the four patients we treated. All received rifampicin in a single daily dose of 450 mg if the body weight was 50 kg or less and 600 mg if the weight was over 50 kg. Isoniazid was given in a single daily dose of 300 mg to two patients who had good renal function, but a lower dose of 200 mg was preferred in a third patient who had persistently elevated blood urea levels of 11–16 mmol/litre during chemotherapy. One patient received ethambutol (25 mg/kg/day) in a single dose for the first two months of chemotherapy and another started on this regimen but changed after four weeks to daily streptomycin and pyrazinamide in addition to rifampicin and isoniazid. No adverse effect from antituberculous therapy was seen in any of these patients.

The risk of isoniazid toxicity in the presence of renal failure is well recognized. It has been suggested (Bowersox et al. 1973) that patients with serum creatinine below 12 mg/100 ml (1060 μmol/litre) can safely receive 300 mg of isoniazid daily and patients with higher creatinine levels should also recieve this dose initially and if necessary have the dose reduced later so that serum concentrations of isoniazid do not exceed 1 μg/ml 24 hours after administration of the dose. These authors suggest that doses of isoniazid below 200 mg daily should rarely be required. Some authorities on the other hand recommend 200 mg daily as the standard dose of isoniazid in normal situations (Crofton & Douglas 1975). We did not attempt to measure serum levels of ethambutol but chose not to prescribe this drug in one patient who had persistently impaired renal function. It is of interest that Ogg et al. (1968) observed toxicity after only 11 g of streptomycin in one patient given the drug thrice weekly after haemodialysis and in whom plasma levels were close to the normal range.

We encountered greater problems in designing a regimen of antituberculosis therapy in our one patient (Case 2) who was also being treated with intermittent haemodialysis. She received rifampicin and isoniazid 200 mg daily (after dialysis on the days when she was dialysed). On the assumption that intermittent high levels of antituberculosis drugs were effective in therapy she also received streptomycin by intramuscular injection twice weekly two hours before haemodialysis. In spite of initially susceptible organisms she responded poorly to antituberculosis therapy and there was evidence of widespread disease at autopsy although she had received chemotherapy for six months before she died. However, *M. tuberculosis* could not be isolated from autopsy material. Stake and Flatmark (1976) briefly describe a patient who died of generalized tuberculosis having received antituberculosis therapy for five months, but give no details of the chemotherapy given.

The three patients who responded to antituberculosis drugs received at least 18 months of therapy. One (Case 4) has had no further therapy and shows no evidence of relapse two years after finishing chemotherapy. Another (Case 3) continued to take isoniazid 300 mg daily for 18 months after completion of combined therapy and has not relapsed in the two years since, and the third (Case 1) completed 18 months therapy and is well one year later. Neff and Hudgel (1973) question the adequacy of a conventional course of 12–24 months on the experience of a single patient who relapsed with isoniazid resistant organisms having received combined chemotherapy for 20 months followed by isoniazid alone for several months thereafter. Their patient had encountered problems of drug intolerance during the early stages of chemotherapy, however, and it would seem more likely that relapse was related to the inadequacy of initial therapy rather than to insufficient duration. There is, at present, no evidence on which to base advice on duration of chemotherapy in immunologically compromised patients.

Prevention

If, as seems likely, tuberculosis occurring after organ transplantation is due to reactivation of previously acquired infection, it might be possible to prevent it. Clearly it is wise to scrutinize the chest radiograph before transplantation for evidence of definite or possible previous tuberculosis. Only one of our patients, however, had an abnormal radiograph. Bilateral apical pleural thickening had been present unchanged for two years and she subsequently developed disseminated tuberculosis. At autopsy the caseous lesion which had ruptured into a bronchus was in the upper lobe. That lesion was not, however, visible on pretransplantation radiographs.

None of our patients had received a tuberculin test before transplantation. It would seem prudent to include tuberculin testing in pretransplantation assessment, although interpretation of the results may be difficult. It is known, for example, that patients undergoing regular haemodialysis may have negative tuberculin skin tests having previously given a positive reaction (Pradhan et al. 1974). A positive tuberculin test in the absence of previous BCG immunization should lead to consideration of prophylactic antituberculosis chemotherapy or should, at least, alert the clinician to the risk of subsequent tuberculosis.

Chemoprophylaxis with isoniazid has been recommended for persons who are positive tuberculin reactors (American Thoracic Society 1974). The additional risk of prolonged therapy with corticosteroids or immunosuppressive therapy is emphasized. It is not known, however, whether the small but real risk of serious adverse effects from isoniazid outweighs the benefits of tuberculosis prevention in such subjects. The incidence of toxicity might be greater than that recorded elsewhere if isoniazid were given before transplantation to tuberculin-positive patients in severe renal failure, and isoniazid could be ineffective or toxic if given to patients receiving regular haemodialysis unless the dosage was adjusted. No further recommendations can be offered on the available evidence.

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A COMPARISON OF ORAL CHOLINE THEOPHYLLINATE AND BECLOMETHASONE IN SEVERE PERENNIAL ASTHMA IN CHILDREN

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Summary

Fourteen children with perennial asthma previously treated with beclomethasone dipropionate were studied for four months in a crossover trial to compare the efficacy of choline theophyllinate and beclomethasone dipropionate aerosol in the control of their symptoms. Assessments were made using twice daily peak flow measurements, together with daily records of symptom scores and use of extra salbutamol. Beclomethasone and oral choline theophyllinate together improved control of asthma in comparison with beclomethasone alone. Reduction of the dose of beclomethasone from 400 μg/day caused worsening of asthma. Oral choline theophyllinate did not prevent this deterioration and therefore cannot replace beclomethasone for the long-term treatment of such asthmatic patients.

INTRODUCTION

Beclomethasone dipropionate aerosol has been used extensively for the treatment of perennial asthma in children (Lal et al. 1972; Morrow Brown & Storey 1973, 1975; Godfrey & Konig 1974). It is effective and when used over long periods in doses up to 1200 μg/day it does not significantly suppress the pituitary-adrenal axis or cause other systemic side effects (Gaddie et al. 1973; Godfrey & Konig 1974; Lovera et al. 1976). Increased incidence of oral and nasopharyngeal candidiasis has been reported as a side effect in adults (McAllen et al. 1974; Willey et al. 1976) and less commonly in children (Lovera et al. 1976).

The principal problem associated with its use in children is that some, particularly the younger ones, find the inhaler difficult to use. This makes effective administration impossible in many cases and the clinician is often forced to prescribe other forms of corticosteroid. It has been suggested that theophylline, if taken regularly, may reduce patients' requirement for beclomethasone (Hambleton et al. 1977) and it is possible that it could be used in place of beclomethasone for the long-term treatment of some of them.

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If this proved to be the case, it would be the drug of choice for use in patients whose symptoms were not adequately controlled by other bronchodilators or cromoglycate.

To assess the value of theophylline in the treatment of severe perennial asthma we have carried out a crossover trial comparing oral choline theophyllinate and beclomethasone dipropionate in a group of asthmatics previously judged to require beclomethasone.

Patients and Methods

Sixteen children aged 8–14 years were studied. They all had perennial asthma and had previously been treated with intermittent salbutamol and sodium cromoglycate. These drugs had failed to control symptoms and before the trial all the patients were taking beclomethasone dipropionate 200–600 μg/day, with additional oral or aerosol salbutamol as necessary. Six had required at least one short course of oral prednisolone during the previous 12 months.

During a pre-trial week the choline theophyllinate dose was adjusted and the patients' beclomethasone inhalation technique was checked. Choline theophyllinate was given as an elixir containing 100 mg choline theophyllinate per 5 ml (65% theophylline) as nearly as possible at 08.00, 13.00, 17.00 and 21.00 hours each day. Initially the children were given 4 mg/kg per dose. After 24 hours the dose was increased to 8 mg/kg and after a minimum of three days serum theophylline was measured using high pressure liquid chromatography (McKenzie et al. 1978). Finger-prick blood specimens were collected two hours after a dose when peak serum concentrations would be expected. If necessary the dose of choline theophyllinate was then adjusted to ensure that the peak concentrations came within the optimum therapeutic range (10–20 μg/ml).

Two children vomited persistently during the pre-trial week despite having low serum theophylline concentrations, and they did not enter the trial.

The patients were studied for four consecutive four-week periods A–D. Half the time they took active choline theophyllinate (Periods A and C) and half the time they took placebo (Periods B and D). During periods A and B they also took standard doses of beclomethasone aerosol two puffs (100 μg) four times daily and during the remaining two periods C and D they attempted to reduce the beclomethasone dose at weekly intervals, omitting it completely if possible in the fourth week of each. Additional aerosol salbutamol was taken in doses up to 800 μg/day as necessary. As an extra safeguard during the reducing periods C and D, the patients were asked to return to the standard dose of beclomethasone if salbutamol failed to control symptoms, or if peak flow (PEF), which was measured twice daily, fell below 50% expected normal (Godfrey et al. 1970) on two consecutive occasions. Drug administration was randomized according to a latin square design and the trial was double-blind with respect to choline theophyllinate. However as it was not considered ethical to stop all aerosol beclomethasone suddenly in these previously dependent patients placebo aerosol was not used. Instead the patients were asked to attempt to reduce the dose of beclomethasone.

Throughout the trial daily records of symptoms and doses of salbutamol taken were kept on diary cards (Connelly & Godfrey 1970). In addition, morning and evening PEF was measured before drugs were taken using the best of three results from a peak flow gauge. The patients were seen at the end of each period, when specific enquiry was made about the occurrence of side effects and finger-prick blood samples were collected for measurement of peak serum theophylline concentrations.

Statistical analysis of the data recorded daily by each child was made using four factor analysis of variance (Cochran & Cox 1957). Thus multiple paired comparisons were made between equivalent days of the four periods.

RESULTS

Choline theophyllinate dose and serum theophylline concentrations

Doses of choline theophyllinate and serum theophylline concentrations of all patients are shown in Table I. The range of serum theophylline concentrations was very wide.

However, for ten patients at least one of the measurements was in the optimum range. Patients 1 and 10 suffered persistent nausea and vomiting when their dose was increased and therefore entered the trial taking suboptimal doses. Five patients had unexplained low serum theophylline concentrations on one occasion.

Table I. Details of patients, choline theophyllinate doses and peak serum theophylline concentration

Patient	*Age* (years)	*Sex*	*Weight* (kg)	*Choline theophyllinate dose* (mg/kg)	*Serum theophylline concentration* (μg/ml)	
					Period A	Period C
1	11	M	25	10	7	6
2*	11	F	39	8	3	9
3*	11	M	31	8	1	6
4	14	M	56	8	9	13
5	5.5	M	21	12	13	14
6*	12	F	32	10	1	14
7	10	M	25	8	7	10
8	13.5	M	33	12	11	11
9*	11.5	F	29	10	10	3
10	11	M	31	8	7	5
11	10	M	39	8	—†	10
12	13	F	42	7.5	—‡	9
13*	9	F	23	12	16	5
14	8	F	24	8	7	8
Mean (all patients)				9.3	8.3	
Range (all patients)				7.5–12	1–16	
Mean (excluding*)					9.2	
Range (excluding*)					6–14	

* Patients with one unexpectedly low serum theophylline measurement during the trial, who may not have taken the dose as prescribed.

† This patient vomited after his morning dose of choline theophyllinate on the morning of the test.

‡ This patient thought she should not take her medications on the morning she attended the clinic.

Treatment effect of beclomethasone

The difference between morning and evening PEF, symptom scores and salbutamol use during periods A and B (standard beclomethasone) and periods C and D (reducing beclomethasone) demonstrated that asthma symptoms and signs were significantly less while the patients were taking full doses of aerosol steroid (Fig. 1). Reduction of the dose of beclomethasone was associated with an increase in symptoms, increased use of salbutamol and a reduction of morning and evening PEF. The differences were all highly significant ($P < 0.002$) when the fourth weeks of the periods were compared.

Treatment effect of choline theophyllinate

Reduction of beclomethasone dose under cover of active choline theophyllinate was followed by a significant increase in symptom scores and daily use of salbutamol. These changes were associated with corresponding falls in morning and evening peak flow (Fig. 2). Comparison of the fourth week of this period with the fourth week of treatment with the standard dose of beclomethasone and placebo showed that choline theophyllinate could not adequately replace beclomethasone. Standard beclomethasone treatment was associated with significantly higher morning and evening PEF ($P = 0.05$, $P = 0.03$) and significantly lower symptom scores ($P = 0.005$). The daily dose of salbutamol used did not differ significantly. Separate analysis of the data from the nine patients in whom there were no unexplained low serum theophylline measurements gave similar results.

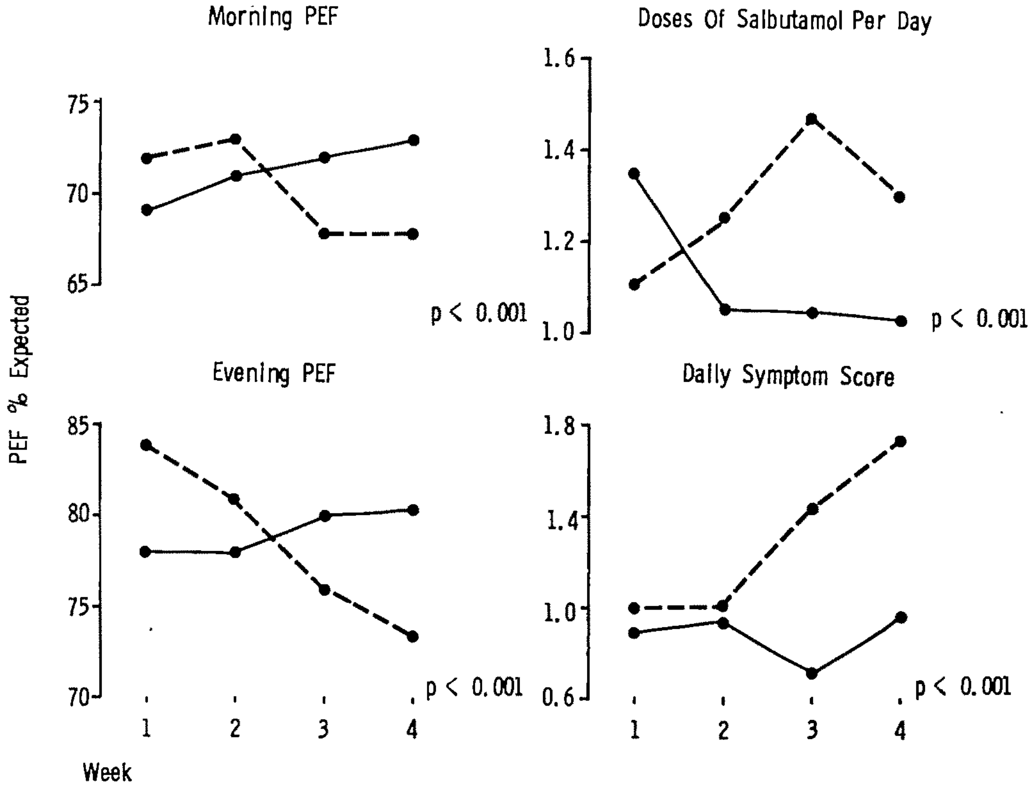

Fig. 1. Treatment effect of beclomethasone dipropionate. ———, Standard periods; - - -, reducing periods. Significance values calculated from comparisons of week 4

Treatment effects of choline theophyllinate and beclomethasone combined

When choline theophyllinate and standard doses of beclomethasone (period A) was compared with standard beclomethasone and placebo (period B), morning and evening PEF were significantly higher ($P < 0.001$, $P < 0.001$, Fig 3). The daily use of salbutamol was also significantly less ($P < 0.001$, Fig. 4). Symptom scores were not significantly different. Analysis of the data for the nine subjects in whom there were no unexplained low serum theophylline measurements and for the whole group gave similar results.

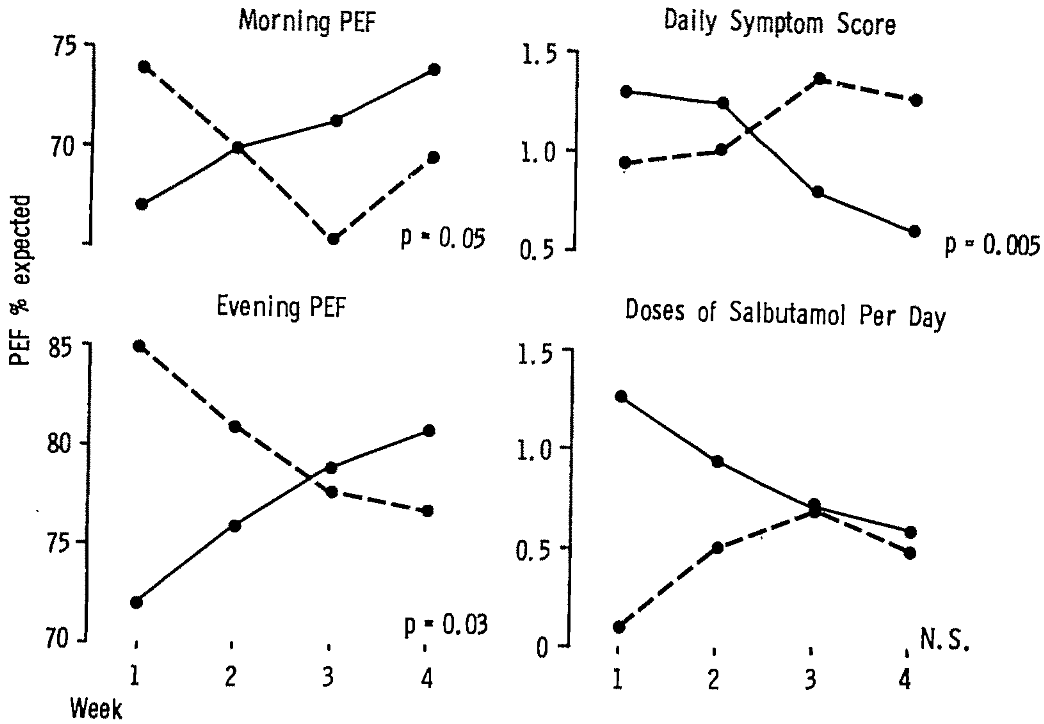

Fig. 2. Treatment effect of choline theophyllinate. ———, Standard beclomethasone and placebo choline theophyllinate; – – –, choline theophyllinate and reducing beclomethasone. Significance values calculated from comparisons of week 4

Adverse effects

Two patients vomited persistently in the pre-trial week and did not enter the trial. Two further patients were unable to tolerate optimum doses of choline theophyllinate because of nausea. Several patients complained of mild gastrointestinal disturbance during the early stages of the trial and one also complained of sleep disturbance. These symptoms did not persist and did not require special treatment. There were no adverse effects from the beclomethasone.

Three patients developed severe attacks of asthma requiring admission to hospital. Patient 1 was admitted twice, first during period D and again during period A. Patient 3 was admitted during period D and patient 9 during period B. The treatment code was broken on these four occasions as the patients required intravenous therapy.

DISCUSSION

This trial has shown that the addition of oral choline theophyllinate to beclomethasone dipropionate for the treatment of children with severe perennial asthma results in a significant improvement in PEF and reduced use of intermittent salbutamol. Therefore it may be a useful addition to therapy for those patients who are not well controlled by

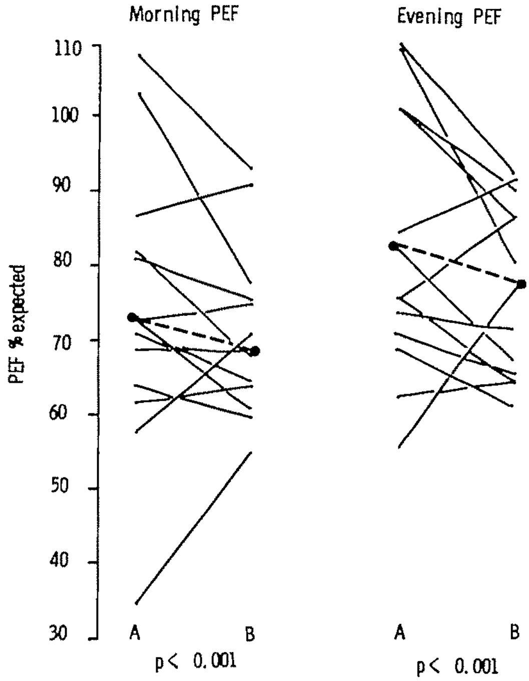

Fig. 3. Treatment effect of beclomethasone combined with choline theophyllinate. A = standard beclomethasone and choline theophyllinate; B = standard beclomethasone and placebo. ———, mean values for each individual; ---, mean for the group. Significance values calculated from the daily records for each child

beclomethasone alone. The results also show that choline theophyllinate will not usually replace beclomethasone dipropionate for the long-term management of such patients as this substitution produced a significant fall in morning and evening PEF and an increase in symptom scores.

Several difficulties associated with the out-patient use of oral theophylline have been highlighted by this study. Most children complained the elixir tasted unpleasant. Older children would normally take tablets or slow-release capsules, which are better tolerated, but these are not suitable for young children, who have most difficulty taking aerosols and for whom theophylline has potentially the most value.

One of the major problems was the achievement and maintenance of optimum therapeutic serum theophylline concentrations. Some bronchodilator response occurs with concentrations as low as 5 μg/ml (Masselli et al. 1970; Mitenko & Ogilvie 1973) but optimum response is generally considered to occur with concentrations between 10 and 20 μg/ml (Mitenko & Ogilvie 1973; Nicholson & Chick 1973). The difficulties arise because of variations in the rate of absorption from the gastrointestinal tract (Welling et al. 1975), variations in rates of clearance from plasma (Ellis et al. 1976) and failure of patients to take the prescribed dose regularly (Eney & Goldstein 1976). It is probable that poor compliance was the major cause of the observed variation of serum theophylline concentration. The patients were asked to take the choline theophyllinate at regular

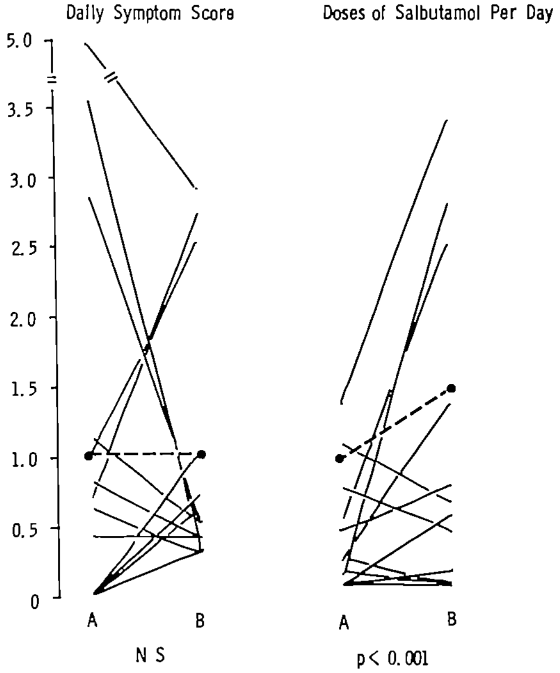

Fig. 4. Treatment effect of beclomethasone combined with choline theophyllinate. A = standard beclomethasone and choline theophyllinate; B = standard beclomethasone and placebo. ———, mean values for each individual; ---, mean for the group. Significance values calculated from the daily records for each child

times each day and to reduce gastrointestinal variation to a minimum, and it is unlikely that individual plasma clearance of theophylline would have altered significantly during the trial period. The poor compliance with prescribed treatment was highlighted here because objective measurements were made when the patients were seen. It is probable that similar problems are common to other drug trials where there is no such objective assessment. This makes interpretation of the results of such trials much more difficult.

In conclusion, this trial has demonstrated that oral theophylline may be a useful addition to the treatment of severe perennial asthmatics whose symptoms are not well controlled by an inhaled corticosteroid and salbutamol. It cannot replace inhaled corticosteroid for the long-term treatment of these patients.

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OBSERVATIONS ON THE MANAGEMENT OF ACUTE BRONCHIAL ASTHMA

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Summary

This survey of acute asthma admissions points to a number of factors that may be relevant to the continuing asthma mortality at home and in hospital.

1. Complications in hospital occur with increasing frequency with increasing pulse rate, but mortality is low with intensive management.
2. Young patients tend to have the higher pulse rates and greater risk of complications.
3. Many patients with severe asthma do not receive adequate drug treatment, particularly corticosteroids, from their general practitioners before admission to hospital.
4. Many severe attacks of asthma come on quickly and these patients are particularly at risk.

INTRODUCTION

There has been little change in the mortality from bronchial asthma in recent years. In England and Wales there were 1245 deaths in 1970, 1198 in 1971 and 1246 in 1972 (Registrar General's Statistical Reviews for England and Wales). In Scotland 412 deaths occurred outside hospital and 176 in hospital during the years 1969 to 1972 (Registrar General's Statistical Reviews for Scotland). Suggestions for preventing deaths from asthma both at home and in hospital have been made by several authors during the past two years (Cochrane & Clark 1975; Crompton & Grant 1975; Fisher & Ghory 1975; MacDonald et al. 1976). This paper reports an attempt by one specialized respiratory unit to identify the factors which could be relevant to the continuing asthma mortality at home and in hospital.

Patients and Methods

The case records of all patients with acute bronchial asthma admitted to the Respiratory Unit of the Northern General Hospital, Edinburgh, between 1970 and 1974 were reviewed retrospectively. Details were extracted of the clinical pattern of the patients' asthma, the duration of acute pre-admission symptoms, the maintenance and emergency treatment received at home and in hospital and the complications which occurred during hospital treatment. The Respiratory Unit serves mainly the adult population of the north of Edinburgh, although a few paediatric patients are also admitted. An Emergency Asthma Admission Service operating for patients considered to be particularly at risk (Crompton & Grant 1975) allows these patients to be admitted direct to the unit without being seen by their general practitioners. All patients in the survey were admitted initially to a respiratory intensive therapy area for assessment and treatment and were later transferred to adjacent medical wards, where the same medical and nursing staff continued their care.

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Two hundred and seventy-six patients, 97 male and 179 female, were admitted on 419 occasions: 98 patients had acute episodic symptoms, and 178 chronic symptoms. Of the 276 patients included in the survey 165 (57%) were new referrals to the unit. At the time of first admission 4% were under 10 years of age, 25% were between 10 and 20 years, 50% were between 20 and 60 and 21% were over 60. Of the total of 419 admissions, 277 (66%) were arranged by general practitioners, 89 (21%) came from the Emergency Asthma Admission Service, 43 (10%) from out-patient clinics and 10 (3%) from other hospitals. Sixty-three patients were readmitted on more than one occasion, and these patients accounted for 206 of the 419 admissions. The frequency of readmission and the time intervals between admissions are shown in Tables I and II. It can be seen that 61 of the 143 readmission intervals were three months or less.

At the time of admission 201 (48%) of patients were receiving systemic corticosteroids, either alone or in combination with other prophylactic drugs, 33 (8%) were being treated with a corticosteroid aerosol by inhalation, and 42 (10%) with sodium cromoglycate. Seventy-seven patients (18%) were taking only bronchodilator drugs, and 66 (16%) were on no treatment.

Table I. Frequency of readmission

No. of admissions	*No. of patients*
1	213
2	29
3	21
4	3
5	4
6	1
7	2
>7	3

Table II. Intervals between readmission

Readmission interval	*No. of readmissions*
< 1 week	1
1–4 weeks	20
1–3 months	40
3–6 months	26
6–9 months	12
>9 months	44

RESULTS

Duration of pre-admission symptoms

The relationship between the heart rate on admission to hospital and the duration of symptoms before admission is shown in Table III. Heart rate was used to gauge the severity of asthma, since it was always recorded in the case records. There are, or course, other methods of grading the severity of attacks of asthma (Jones 1971) and these may be more reliable, but the need for immediate treatment precluded their use in most of the patients included in this survey. Table III shows that the majority of patients with

Table III. Duration of symptoms before admission

Heart rate (beats/min)	*Duration of symptoms* (days) One or less (%)	>1–3 (%)	>3 (%)	Not known (%)	*No. of admissions*
⩽90	20	15	65	0	35
>90–110	29	18	51	2	120
>110–130	41	17	29	3	148
>130–150	40	22	34	4	82
>150	59	12	26	3	34

heart rates of less than 110/minute had had symptoms for several days, whereas most of those with a heart rate of more than 150/minute had had symptoms for 24 hours or less.

Relationship of heart rate on admission to age (Table IV)

There was a higher proportion of patients with severe tachycardia below the age of 20 than in older patients. There must be many reasons for this, but it is the younger patients who develop the most severe attacks of asthma, with high complication rates. There were 157 (37%) of admissions in age range 0–20 years, and these accounted for 59% of all admissions with a heart rate greater than 150/minute.

Table IV. Relationship of heart rate on admission to age

Heart rate on admission (beats/min)	*Age group* (years) 0–20	>20–40	>40–60	>60	*Total admissions*
⩽90	5 (14%)	9 (26%)	12 (34%)	9 (26%)	35
>90–110	30 (25%)	36 (30%)	23 (19%)	31 (26%)	120
>110–130	59 (40%)	33 (22%)	32 (22%)	24 (16%)	148
>130–150	43 (52%)	22 (27%)	13 (16%)	4 (5%)	82
>150	20 (59%)	13 (38%)	0 (0%)	1 (3%)	34
Total admissions	157 (37%)	113 (27%)	80 (19%)	69 (17%)	419

Emergency pre-admission treatment

The treatment received by patients admitted by their general practitioners is shown in Table V. The heading 'Systemic Corticosteroid' refers either to an increase in dose given to patients on regular maintenance corticosteroid therapy or to a first course in those not receiving such treatment. Many patients were not given bronchodilator drugs or corticosteroids, either intravenously or by mouth, before they were transferred to hospital.

In Table VI the admissions have been divided into new patients and those already under supervision. More patients in the second group were on regular corticosteroid therapy than were new patients, and more of them also received emergency treatment with corticosteroids when the heart rate exceeded 110/minute. However, only 50% of all patients who were on regular corticosteroid therapy had the dose increased before they were admitted to hospital.

Table V. Treatment of acute episode prior to admission. General practitioner admissions

Heart rate (beats/min)	*Theophylline* (i.v./i.m.) (%)	*Systemic corticosteroid* (%)	*Antibiotic* (%)	*Sedation* (%)	*None* (%)	*No. of admissions*
⩽90	23	17	57	3	10	30
>90–110	26	24	38	3	22	79
>110–130	34	39	40	4	13	98
>130–150	29	50	29	4	13	48
>150	23	41	45	5	9	22

Table VI. General practitioner admissions: corticosteroid treatment

Heart rate (beats/min)	*New referrals*			*Patients already under supervision*		
	No.	Regular corticosteroid	Emergency corticosteroid	No.	Regular corticosteroid	Emergency corticosteroid
⩽90	15	13%	0%	15	60%	33%
>90–110	36	11%	22%	43	63%	26%
>110–130	38	18%	29%	60	58%	45%
>130–150	13	23%	23%	35	66%	60%
>150	12	17%	17%	10	60%	70%

In-patient management

All patients had a chest radiograph on admission and ECG monitoring in the intensive therapy area. Oxygen was administered normally by a 35% Ventimask unless there was clinical suspicion of carbon dioxide retention. Arterial blood gas studies were carried out when indicated clinically. Dehydration was corrected by intravenous infusion when necessary.

Drug treatment during the first 24 hours is summarized in Tables VII and VIII. All adult patients received a 0.5% salbutamol aerosol by intermittent positive-pressure

Table VII. Initial treatment of acute episode in hospital

Heart rate (beats/min)	*Salbutamol aerosol by IPPV* (%)	*Hydrocortisone* (i.v.) (%)	*Aminophylline* (i.v.) (%)	*Antibiotic* (%)
⩽90	100	11	6	71
>90–110	100	26	5	67
>110–130	100	60	14	81
>130–150	100	74	27	73
>150	100	97	15	82

Table VIII. Corticosteroid treatment of acute episode in hospital in the first 24 hours

Heart rate (beats/min)	*24-hour prednisolone dosage* (mg)				*Increase in dose of corticotrophin*	*No treatment with corticosteroid or corticotrophin*
	<20	>20–40	>40–60	>60		
⩽90	6%	11%	29%	0%	6%	48%
90–110	2%	31%	36%	1%	8%	22%
>110–130	2%	27%	51%	2%	11%	6%
>130–150	1%	16%	48%	7%	27%	1%
>150	0%	9%	50%	12%	29%	0%

ventilation (Bennett Therapy Unit) for three minutes at an inspiratory pressure of 15 cm of water, and this was repeated every 2–4 hours, if required, for the first 24 hours. Hydrocortisone was given in a bolus intravenous dose of 100–500 mg immediately after admission, but this was repeated only if the patient was unable to take an oral corticosteroid because of vomiting or artificial ventilation. Those patients with rapid heart rates who were not given hydrocortisone on admission had either received it shortly before from their general practitioners, or had responded so quickly to salbutamol by IPPV that only an oral corticosteroid preparation was required. Where the doses of prednisolone are shown to be less than 20 mg/day, these had all been given to children. Aminophylline (250 mg) was injected slowly intravenously when it was considered that there had not been a good clinical response to the repeated administration of a salbutamol aerosol.

Hospital complications

Of the 52 hospital complications shown in Table IX, 38 (75%) were recorded in patients with a heart rate on admission of above 130/minute. This table also shows that the frequency of hospital complications in relation to the number of admissions increased from 5% when the heart rate on admission was 130/minute or below to 29% when it was above that figure and to 44% when it was above 150/minute.

Table IX. Hospital complications

Complication	*Heart rate* (beats/min)			*Total*
	$\leqslant 130$	$>130–150$	>150	
Unilateral pneumothorax	1	0	0	1
Bilateral pneumothorax	0	0	1†	1
Mediastinal emphysema	1	8	2	11
Lobar collapse	1	1	0	2
Artificial ventilation	1	2	4	7
Cardiac arrest	1	1*	1†	3
Death	0	1*	1†	2
$P_{a}CO_2 > 6$ kPa and pH < 7.35	9	11	8	28
No. of complications	14	23	15	52
No. of admissions	303	82	34	419
Complications as percentage of admissions	5%	29%	44%	21%

* Case 1 } see text
† Case 2 }

There were two hospital deaths, representing a mortality of less than 0.5% of all admissions. *Case 1* was a 50-year-old woman with a major degree of irreversible airway obstruction and severe epilepsy. She was included in the survey because on previous occasions her FEV_1 had risen considerably after treatment with prednisolone, but on this admission there was no improvement, she developed severe carbon dioxide retention three weeks later, and it was not considered that further resuscitative measures were indicated. *Case 2* was a 30-year-old woman who initially responded well to treatment, but suddenly became acutely breathless 36 hours after admission, and had a cardiac arrest.

During resuscitation a pneumothorax was found on the left side when the chest was opened for internal cardiac massage. At autopsy a pneumothorax was also present on the right side. In another patient cardiac arrest occurred shortly after the administration of a salbutamol aerosol by intermittent positive-pressure ventilation, but the heart restarted with a single blow on the chest. This patient had consumed the contents of two pressure-packed aerosol canisters of adrenaline and atropine in the 24 hours before admission.

Seven patients were intubated and ventilated (ages range 13–49 years, five being under 30). One patient with a heart rate on admission of between 110 and 130/minute had already been intubated, and was being ventilated on transfer from another hospital; all the others had heart rates on admission of greater than 130/minute. Eleven patients had mediastinal and/or subcutaneous emphysema; on no occasion did this give rise to any respiratory or circulatory disturbance.

The full results of the arterial blood gas studies are not reported in this paper since the changes which occur in bronchial asthma are well documented (Flenley 1971). Only one patient was admitted in the late stages of severe asthma with bradycardia and acute ventilatory failure. There were three patients with minor degrees of metabolic acidosis. A few patients had evidence of chronic carbon dioxide retention, but because their airway obstruction was partially responsive to corticosteroids they were classified as suffering from bronchial asthma.

Discussion

Our results showed that the greatest degrees of tachycardia occurred in young patients with a duration of acute symptoms of one day or less before admission and that the incidence of major complications in hospital was greatest in those with heart rates on admission of greater than 130/minute. While there are dangers in using this one index to grade the severity of an acute attack of asthma, there would seem to be a strong case for admitting immediately to hospital every patient with a heart rate during an attack of asthma of greater than 130/minute. The same policy should, of course, be adopted in patients with lower heart rates who have severe respiratory distress, central cyanosis, profound exhaustion, dehydration, a 'silent' chest, pulsus paradoxus or a very low peak expiratory flow rate.

There is general agreement that corticosteroid therapy in massive dosage is mandatory in all cases of severe asthma and that the earlier it is started the better, since there is inevitably a delay of a few hours before it becomes effective. It was therefore surprising to find in this survey that over half of all admissions with a heart rate of over 130/minute had received no emergency corticosteroid therapy from their general practitioners; in this respect new patients were particularly at risk. In addition, only about 30% of patients admitted at the request of general practitioners had received a parenteral bronchodilator before transfer to hospital. It is difficult to avoid the conclusion that many doctors fail to grasp the vital importance of decisive drug therapy in severe asthma.

If patients with severe asthma reach hospital alive, and adequate facilities are available for resuscitation, a fatal outcome can almost invariably be averted. In this survey the hospital mortality was less than 0.5% and one of the two deaths might not have occurred if the complication of tension pneumothorax had been recognized at an earlier stage. Most patients responded rapidly, and in some cases dramatically, to the administration of a 0.5% salbutamol aerosol by IPPV and there was no firm evidence to support the view expressed by Karetzky (1975) that this form of treatment was dangerous, since it was given to every patient, and all but two survived. Indeed, our earlier experience suggested that without it many more patients would have required orotracheal intubation and mechanical ventilation. It was, however, appreciated that some increase in the degree of hypoxaemia might follow the administration of bronchodilator drugs, and care was always taken to ensure that all patients were well oxygenated before they were given salbutamol by IPPV. While the outcome of a severe attack of asthma is finally determined by the response to intravenous and oral corticosteroid therapy, the patient's immediate survival will often depend on the effective application of other measures to relieve airway narrowing and hypoxaemia, which in this survey included oxygen therapy, the administration of a salbutamol aerosol by IPPV and, when necessary, orotracheal intubation and mechanical ventilation.

Perhaps the most important single factor in preventing death from severe asthma in the patients of this survey was admission to hospital in good time. The mortality in this survey might well have been much higher but for the operation of the Edinburgh Asthma Admission Service (Crompton & Grant 1975).

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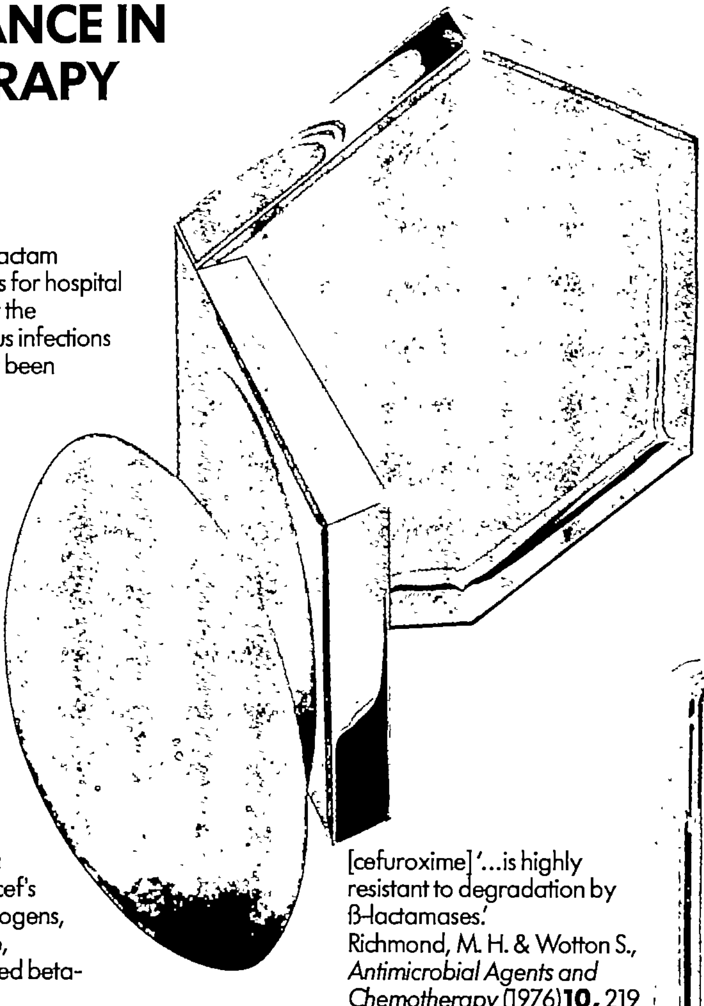

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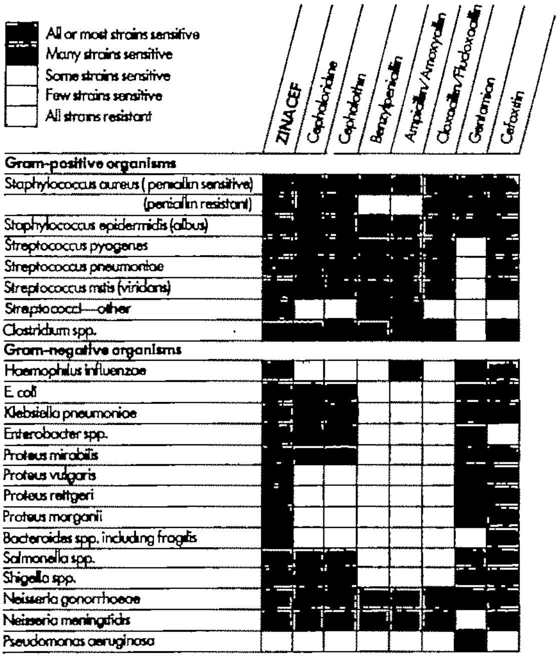

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□ Some strains sensitive
□ Few strains sensitive
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(penicillin resistant)	■	■	■	□	□	■	■	■
Staphylococcus epidermidis (albus)	■	■	■	■	■	■	■	■
Streptococcus pyogenes	■	■	■	■	■	■	□	■
Streptococcus pneumoniae	■	■	■	■	■	■	□	■
Streptococcus mitis (viridans)	■	■	■	■	■	■	□	■
Streptococci—other	■	□	□	■	■	□	□	□
Clostridium spp.	■	■	■	■	■	■	□	■
Gram-negative organisms								
Haemophilus influenzae	■	□	□	□	■	□	■	■
E. coli	■	■	■	□	□	□	■	■
Klebsiella pneumoniae	■	■	■	□	□	□	■	■
Enterobacter spp.	■	■	■	□	□	□	■	□
Proteus mirabilis	■	■	■	□	□	□	■	■
Proteus vulgaris	■	□	□	□	□	□	■	■
Proteus rettgeri	■	□	□	□	□	□	■	■
Proteus morganii	■	□	□	□	□	□	■	■
Bacteroides spp. including fragilis	■	□	□	□	□	□	□	■
Salmonella spp.	■	■	■	□	□	□	■	■
Shigella spp.	■	■	■	□	□	□	■	■
Neisseria gonorrhoeae	■	■	■	■	■	■	■	■
Neisseria meningitidis	■	■	■	■	■	■	□	■
Pseudomonas aeruginosa	□	□	□	□	□	□	■	□

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Br. J. Dis. Chest (1979) *73*, 164

INHALED CORTICOSTEROID AEROSOLS AND CANDIDIASIS

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Summary

A three-month controlled study was performed to assess the cumulative incidence of oral *Candida* carriage and thrush in patients starting to take betamethasone valerate aerosol (800 μg/day) for control of their asthma. Four of 41 patients on the corticosteroid aerosol developed thrush compared with none of 40 in the control group. However, the number of cumulative saliva culture positives for *C. albicans* rose by a similar amount (approximately 20%) in each group. A simple mouthwash procedure was shown to have no prophylactic benefit in the aerosol group. Oral candidiasis was not, however, clinically important.

Introduction

The preliminary Report of the Brompton Hospital/Medical Research Council Collaborative Trial (1974) included details of a high incidence of oropharyngeal candidiasis in those patients transferring from corticosteroid tablets to inhaled beclomethasone dipropionate. Over a 28-week period, with four-weekly assessments, 45% of those taking 400 μg beclomethasone per day developed candidiasis, as did 77% of those on 800 μg per day. The majority of infections were noted within 12 weeks of starting treatment. These data have been criticized (Grant et al. 1974). By including only cases with definite clinical signs and positive throat swabs, the figures are still high, being 33% and 71% respectively (Turner-Warwick & Fox 1974). Others authors have not found such a high incidence although reports have generally indicated prevalence only (Milne & Crompton 1974; Willey et al. 1976) or symptoms only (McAllen et al. 1974). The incidence appears to be similar for both beclomethasone dipropionate and betamethasone valerate (McAllen et al. 1974; Dash 1974; British Thoracic and Tuberculosis Association 1976).

Our experience had not led us to expect such high figures as those reported by the Brompton Hospital Group so we performed a similar study to assess the incidence in our patients. Aerosols of drugs for inhalation behave mainly as though they were swallowed (Dollery et al. 1971) and a large proportion of the dose is deposited in the mouth (Paterson et al. 1968; Swenson et al. 1977). We therefore attempted to decrease the incidence of *Candida* carriage and hence of thrush by rinsing the mouth immediately after aerosol inhalation. Patients in our study used betamethasone valerate aerosol to facilitate distinction between them and other patients in the asthma clinic, most of whom were using beclomethasone dipropionate.

Patients and Methods

Aerosol group

Out-patients starting to take corticosteroid aerosol for the first time for their asthma were admitted to the study. Details were recorded concerning age, sex, wearing of dentures, prescription antibiotics and use of contraceptive steroids. Those with conditions which might variably influence oral *Candida* carriage were not considered; this included patients with oral disease, diabetes mellitus and pregnancy and also patients taking corticosteroid tablets whose dose of such drugs might be changing throughout the study.

Control group

Out-patients attending the Respiratory Function Laboratory for assessment of asthma or shortness of breath, and who were not taking tablet or inhaled steroids, were used as control subjects. Similar details were recorded.

Trial design

All patients including those in the control group were seen initially and at 4, 8 and 12 weeks. At each visit an inspection of the mouth and pharynx was made and patients were questioned about throat symptoms and prescription of antibiotics.

The patients taking the corticosteroid aerosol (800 μg betamethasone valerate/day) were randomly allocated to one of two regimens. The group on Regimen 1 was instructed to take two puffs of betamethasone aerosol four times a day, i.e. after each meal and last thing at night. The group on Regimen 2 took the same dose, but in addition they were told of the 'importance of' removing the corticosteroid from the mouth and so to rinse the mouth thoroughly several times with water immediately after inhalation; they were then to clean their teeth but if this were not possible (e.g. lunch-time) the dose of aerosol was to be taken before this meal so that food might remove the corticosteroid from the gum margins. Patients in either group who wore dentures were told to clean them each night. Sheets with these instructions and also instructions concerning the use of the aerosol were given to each patient. Patients were questioned at each visit about the use of the aerosol and adherence to the regimen.

Microbiological methods

In order to minimize the differences in isolation rates of *Candida albicans* due to diurnal variation (Williamson 1972) patients were interviewed at the same time of day on follow up visits as at the initial visit. At each visit mouth-rinse specimens using 2 ml of saline were taken to establish *Candida* carriage. The minimum volume which could be used to obtain a suitable specimen mixed with saliva and which could be swilled round all parts of the mouth and gargled to reach posterior parts and the soft palate was 2 ml. This was collected into a sterile container and cultured within two hours of collection.

Specimens were cultured into solid Sabouraud's medium using a standard loop, and the remainder inoculated into Sabouraud's broth, which after five days incubation was subcultured onto a Sabouraud plate. The identity of all yeasts isolated was established by germ-tube and biochemical testing.

Smears of suspect mouth lesions were taken with a dry cotton wool bud on a stick and slides prepared. These were fixed, stained by Gram's method and examined for yeasts and hyphae. Only isolation of *C. albicans* was considered relevant to the diagnosis of thrush, other yeasts being ignored for the purposes of this study.

Lesions of the oropharynx were considered to be thrush only if they fulfilled the following criteria:

1. White patches or plaques on examination.
2. Culture of *Candida albicans* from a saliva specimen and also preferably with (3).
3. Demonstration of fungal hyphae on a smear made from the lesions.

RESULTS

Initial assessment

Ninety-seven patients were seen (all groups). None had thrush at their first visit. *C. albicans* was isolated from saliva specimens in 38. There was no significant correlation between denture wearing, sex, or increase in age with *Candida* carriage (Table I); too few were taking antibiotics or contraceptive steroids for useful comparisons to be made.

Follow-up

Details of patients completing the study are given in Table II (four on Regimen 1, six on Regimen 2 and six in the control group did not attend for all the follow-up visits). In the control group, 24 of those completing had asthma. Unfortunately, the aerosol groups were not well matched for initial presence of *Candida* in saliva.

Table I. Features on initial assessment (all patients)

	Total	*With C. albicans*
No. of patients	97	38 (39%)
No. of females	53	16 (30%)
No. of males	44	22 (50%)
No. with dentures	37	17 (46%)
No. without dentures	60	21 (35%)
Age group (years)		
<20	9	4 (44%)
20–39	24	15 (62%)
40–59	35	12 (34%)
>60	29	7 (24%)

Table II. Details of patients completing the study

Group	*No. completing*	*Average age* (years)	*Sex M/F*	*Initial positive culture*	*Cumulative positive culture*	*Change in positive cultures* (%)
Control	40	51	28/12	14 (29%)	21 (52%)	23
Regimen 1 (no wash)	19	45	10/9	5 (26%)	9 (48%)	22
Regimen 2 (mouth-wash)	22	47	15/7	10 (45%)	14 (64%)	19

Two patients on each regimen developed thrush; details are given in Table III. Only one of these patients had symptoms, which did not persist; however, the signs remained and this may have been related to the fact that he received antibiotics mid-study. In the other three instances, the lesions cleared spontaneously and in none of the four was antifungal treatment given.

Four patients on each regimen who had negative cultures initially later had positive cultures and in two, the coincidental prescription of antibiotics seemed related to this. In the control group none developed thrush and seven converted from negative to positive for *Candida* carriage at some stage. Thus at the end of the study the cumulative total for *Candida* carriage was about 20% higher than initially in each group (Table II).

Table III. Details of patients developing thrush on betamethasone valerate 800 μg/day

Regimen	*Age*	*Sex*	*Possible predisposing factor*	*C. albicans first visit*	*Lesion first noted*	*Progress*
No wash	44	F	None	No	3 weeks	Present at 8 weeks Cleared by 12 weeks
No wash	53	M	Dentures Antibiotics at 6–8 weeks	Yes	3 weeks	Signs persisted
Mouth-wash	49	F	Dentures Oxytetracycline at time of starting aerosol	Yes	4 weeks	Cleared by 8 weeks
Mouth-wash	33	M	Dentures	Yes	8 weeks	Cleared by 21 weeks

DISCUSSION

Our trial was similar in design to the study performed by the Brompton Group. However, our cumulative incidence of thrush infection after three months was 10% compared with 30–60% at this time in the Brompton Study. The only other study to assess *Candida* carriage and thrush in a similar way (Toogood et al. 1977) showed that, at the end of eight weeks and with doses of beclamethasone aerosol increasing from 200 μg, 400 μg and 800 μg to 1600 μg at two-weekly intervals with assessments two-weekly, the prevalance of thrush was about 15% and *Candida* carriage rose 25%, from 35% to 60%. These figures were more like our own, including the rise in culture positives, although a similar rise in culture positives occurred in our control group.

Candidiasis seems to be a local response since patches of thrush were seen on areas where the aerosol is likely to have been deposited. Further, the systemic effects of these corticosteroid aerosols are not detectable within the usual therapeutic range. In addition, these local effects are dose related (Brompton/MRC 1974; Toogood et al. 1977). A mouth-washing procedure, such as performed by half our aerosol group, reduces the amount of corticosteroid in the mouth to very low levels, i.e. lower than a reduction in dosage would achieve (S. M. Harding, personal communication). We were therefore surprised that this procedure seemed to have no influence on the development of thrush. An explanation for these observations would be that the local binding or uptake of corticosteroid occurs very rapidly, that this is proportional to dose, and that the corticosteroid is not recovered by water mouth-wash performed even 'immediately' after dosing. Since the corticosteroid aerosols now in common use are very water insoluble, the rinsing procedure would only remove surface corticosteroid in suspension. The suggestion by McAllen and colleagues (1974) to wash out the mouth may therefore not be helpful. A reduction in dosage might be of benefit if thrush appears. In none of our patients was thrush or oral candidiasis clinically important.

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TWO AMINOPHYLLINE PREPARATIONS IN NOCTURNAL ASTHMA

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Summary

In a double-blind trial the effects of aminophylline suppositories and slow-release aminophylline tablets were compared with similar placebo preparations in nine patients whose complaint was asthma which woke them from sleep at night. Forced expired volume in one second (FEV_1) was measured in each patient at three-hourly intervals from 1900 hours to 0700 hours on four separate nights, the preparation being administered immediately after the 2200 hour measurement. On the nights when a placebo was administered the FEV_1 showed a statistically significant fall between 1900 and 0400 hours. Aminophylline had a statistically highly significant effect in reducing or preventing this fall, suppositories and tablets being equally effective in this single-dose study.

Introduction

Patients can be awakened from sleep in the early hours of the morning by asthmatic wheezing which may last for an hour or two, usually relieved by a β-sympathomimetic bronchodilator aerosol (Hetzel et al. 1977).

The reduction in peak flow which occurs in asthmatics seems to be an exaggeration of a similar circadian variation which has been shown to occur in healthy people (Reinberg & Gervaise 1972). Turner-Warwick (1977) has drawn attention to the importance of this variation in peak flow in asthmatics recovering from a severe attack since it appears to be an indicator of serious instability which can lead to sudden death after severe attacks. The same author proposes that slow-release preparations of β-sympathomimetic agents may be effective in preventing the early morning reduction in peak flow, but little published evidence supports this suggestion.

The aim of the present investigation was to measure and compare the effect of two aminophylline preparations in preventing nocturnal wheeziness. The study was carried out on a group of ambulant patients whose main complaint was asthma which woke them from sleep.

Patients and Methods

The 10 patients studied were chosen from those attending a chest clinic for the main symptom of wheeziness which woke them from sleep in the early hours of the morning. Patients with productive cough and those taking corticosteroids were excluded, but all of them were receiving drugs which included salbutamol, choline theophyllinate, disodium cromoglycate and slow-release aminophylline tablets. There were eight women and two men, of whom all but one (Case 6) were atopic subjects (ages 20 to 62 years, mean 38 years). All gave informed consent to the study.

The aminophylline preparations used in this study were aminophylline suppositories (two suppositories each containing 360 mg of aminophylline) and slow-release aminophylline tablets (two tablets each containing 225 mg of aminophylline). Forced expired volume in one second (FEV_1) was measured using a Vitalograph, the best of three successive forced expirations being recorded.

Each patient spent two nights in hospital on each of two succeeding week-ends, returning home to lead a normal life during the intervals. During the day-time the patients continued to take their regular bronchodilator medication except that the two individuals taking slow-release aminophylline tablets were asked to discontinue this preparation at least eight hours before beginning a nocturnal test. All theophylline-containing beverages were forbidden for at least four hours before beginning a test. A double-blind study of the effect on FEV_1 of two aminophylline suppositories compared with two placebo suppositories was carried out on the two successive nights of one week-end, and of two slow-release aminophylline tablets and two placebo tablets on the two successive nights of the other week-end. Each patient was allocated randomly to one of 10 predetermined schedules which ensured that equal numbers of patients would receive the suppository or the tablet first, and that equal numbers would receive the placebo before the active preparation or *vice versa*.

On each test night the patient came to the hospital at 1800 hours and measurements of FEV_1 were made at three-hourly intervals during the night beginning at 1900 hours. Immediately after the 2200 hours measurement the aminophylline preparation (or placebo) was administered and the patient retired to bed. FEV_1 measurements were made throughout in the sitting position beside the bed, the patient returning to bed as soon as each measurement had been recorded. After the last measurement at 0700 hours the patient returned home to normal activities. Any complaints of symptoms or side-effects from the treatment were recorded at the time.

RESULTS

All the patients remained symptomatically stable throughout the period of study, but one withdrew after the first week-end because she complained of nausea which she attributed to the treatment. One patient completed the study but, in spite of repeated practice, was unable to carry out the forced expiratory manoeuvre successfully and her results were discarded. The results summarized below therefore constitute the values obtained in nine patients, one of whom only completed the trial with the suppositories. The findings were analysed statistically using the student *t*-test and by analysis of variance.

Fig. 1 illustrates the change in FEV_1 from the initial measurement at 1900 hours (ΔFEV_1), showing the mean of the values obtained in all patients at each three-hourly measurement on the nights when a placebo preparation was administered, with the standard error of the mean for each measurement. There was a significant difference between the means ($P < 0.001$) for each measurement except between the means of the 0400 hours and 0700 hours measurements which were not significantly different. Fig. 2 shows the mean values for ΔFEV_1 in all patients at each three-hourly measurement, illustrating the effect of the placebo compared with the active preparation given immediately after the 2200 hours measurements. The mean values obtained at 0100, 0400 and 0700 hours differed significantly between the placebo and the active preparations ($P < 0.001$) both for the suppositories and for the tablets, but there was no significant difference between the effect of the suppositories and that of the tablets.

DISCUSSION

The patients studied were chosen on the basis of their clinical history of nocturnal wheezing, and all except one (Case 6) gave evidence of a substantial degree of airway

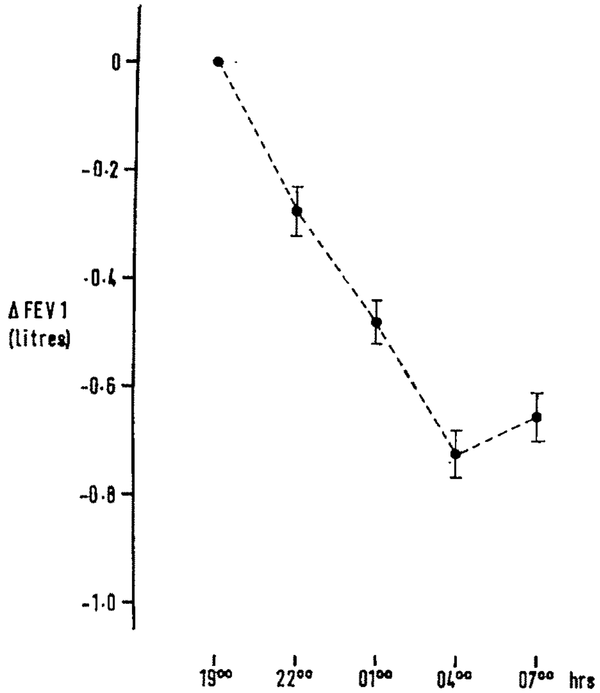

Fig. 1. Mean change in FEV1 (litres ± SEM) from the initial measurement at 1900 hours in nine patients on the nights when a placebo preparation was administered

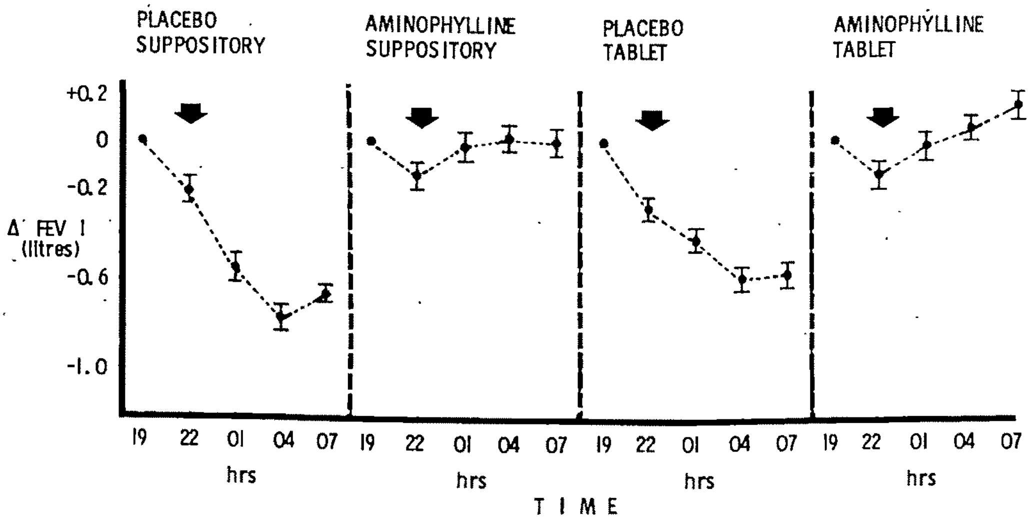

Fig. 2. Mean change in FEV1 (litres ± SEM) from the initial measurement at 1900 hours in nine patients, illustrating the effect of the active aminophylline preparations in preventing the fall in FEV1 which occurred when a placebo preparation was administered

narrowing during the early hours of the morning as shown by the change in FEV_1 which was recorded on the nights when they received a placebo preparation. This airway narrowing was prevented or reduced when aminophylline was administered either by the oral or the rectal route.

Side-effects were few. Case 2 withdrew half-way through the study because of nausea but she did not incriminate the active preparation any more than the placebo. One other patient complained of headache and nausea on the morning after he had received a placebo tablet. All patients preferred the oral preparation of aminophylline. None experienced any rectal irritation or discomfort from the suppository.

Although the effect produced by aminophylline on the FEV_1 showed a similar trend in all the patients studied, there was considerable variation in the magnitude of this effect between patients, and some individuals showed a greater change in FEV_1 with one preparation than with the other. This variability may be attributable to difference in the rate and extent of absorption of the drug from the two sites of administration, or to changes in the patients' condition.

These results suggest that slow-release aminophylline tablets and aminophylline suppositories can prevent nocturnal wheezing. Further studies would be necessary to show whether the same preparations would control the unstable phase of nocturnal airway narrowing which can occur during recovery from an acute attack of asthma, and whether the effects persist with continued medication.

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MALIGNANT PLEURAL EFFUSIONS AND THEIR TREATMENT BY INTERCOSTAL TALC PLEURODESIS

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An analysis is presented of 44 patients with malignant pleural effusion treated by intercostal talc pleurodesis, all except eight of them between 1966 and 1971.

Patients and Methods

The patients were 16 men (mean age 61 years) and 28 women (mean age 60 years). The sites of the primary cancer were as shown in Table I.

The group of primary cancers of the lung has some features of special interest. First, 14 of the patients were women and only 13 were men, whereas the sex ratio for all cancers of the lung in this region is 6:1 preponderance in men (Harley 1976). It thus appears that cancer of the lung is much more likely to give rise to malignant pleural effusion in women than in men.

All the effusions were deemed to be malignant and to have contraindicated operation for the tumour. The effusion was on the right side in 21 cases, on the left side in 19 cases and on both sides in four cases. Only one bilateral effusion was caused by primary cancer of the lung.

Table I. Site of the primary cancer in the 44 cases described

Primary site of cancer		*No. of cases*
Lung		26
Pleura (mesothelioma)		1
Other sites		17
Breast	6	
Ovary	4	
Uterus	1	
Prostate	1	
Thymus	1	
Stomach	1	
Larynx	1	
Bone (osteogenic sarcoma)	1	
Myeloid leukaemia	1	
Total		44

The effusion was serous at first in 18 patients, but became blood-stained later in two of them. It was blood-stained from the beginning in 22 patients and was chylous in one, the man with myeloid leukaemia. The nature of the liquid was not ascertained in four cases. Malignant cells were found in 30 effusions. The protein content was above 3 g/100 ml in 22 out of the 23 cases investigated, ranging from 3.2 to 5.5 g/100 ml, with an average of 4.5.

Management

Thirty-six of the 44 patients were treated during the six-year period 1966–71. Before pleurodesis 163 aspirations were performed on 43 of the 44 patients, an average of 3.8 aspirations per patient. The total amount of liquid withdrawn before or at pleurodesis could be estimated in the case of 37 patients and was found to be an average of 5 litres per patient.

Of the 44 patients treated, pleural symphysis was achieved in 31 (70%) while 13 (29%) had evidence of a residual effusion. Of the latter 13 only four (9% of the total) required either aspiration or a second poudrage, and in eight of the remaining nine the effusion was non-progressive. Thus in 90% of the patients the pleural effusion was either eliminated by pleural symphysis or controlled and rendered non-progressive, presumably by pleural fibrosis, so that no further treatment was required.

Survival after talc pleurodesis for malignant pleural effusions

Thirty-eight of the 44 patients are known to have died, three are alive (1977), and three have been lost to follow-up.

All three patients who are alive are afflicted with cancer of the breast. Two of them are surviving at one year and nine months, the third at six years and nine months. None of them has required aspiration or a second pleurodesis.

Control of pleural effusion in patients living more than six months after pleurodesis was excellent. Only two of these required aspiration or a second pleurodesis. One, with a carcinoma of the lung, had a single aspiration of 500 ml of dark brown liquid four days before his death, seven and a half months after pleurodesis.

Technique

My technique is as follows. General anaesthesia is administered through an endotracheal tube to the patient who is in lateral decubitus. One intercostal cannula is inserted into the axilla via the fifth or sixth intercostal space and a second just behind the angle of the scapula. The effusion is completely evacuated with a sucker, the lung is inspected with a telescope and a pleural biopsy specimen is taken if required. The entire surface of the visceral and parietal pleura is then insufflated through both cannulae with an RAF-type insufflator, using 5–10 g of iodized talc, prepared as described by Jones (1969). Drainage tubes are inserted through each cannula and connected to a source of negative pressure sufficient to keep the lung fully expanded (normally 30–50 mmHg, but up to 250 mmHg may be required). The tubes are removed when the lung has been fully expanded without air leakage for 48 hours and when there is no appreciable leakage of liquid. This is usually after three or four days, occasionally after more than a week.

DISCUSSION

The incidence of pleural effusion in malignant disease

About one-half of women with carcinoma of the breast develop a malignant pleural effusion (Ultmann 1962). Lowell (1959) showed that 25% of 1231 pleural effusions were due to various new growth while Leuallen and Carr (1955) found metastatic carcinoma to be responsible for 52% of 436 effusions. The incidence of a malignant cause for effusions depends largely on the type of patients surveyed and different figures vary between 10 and 50% (Ultmann 1962). Amongst 360 cases of carcinoma of the bronchus Brinkman (1959) found 21 (6%) with pleural effusion, but no other evidence of inoperability. Vieta and Craver (1941) found that 29% of patients with Hodgkin's disease had pleural involvement at autopsy and that 16% of them had had effusions during the course of their disease. They found the incidence of pleural effusion in lymphosarcoma to be 17%. Bruneau and Rubin (1965) reported a 33% incidence in 64 cases of malignant lymphoma. An effusion may be the first indication of malignant disease, or occur as a complication at any stage in a previously diagnosed case.

Talc pleurodesis

A number of irritants applied to the pleura have been used to promote pleural adhesions. The most successful of these is talc. This was first used in man by Bethune (1935) to promote pleural adhesions before lobectomy. Talc has been used for many years in the treatment of spontaneous pneumothorax. It has been shown to be the most effective material for producing pleural adhesions (Singer et al. 1941; Frankel et al. 1961; Smith & Rothwell 1962; Pearson & MacGregor 1966; Jones 1969). It creates effective pleural symphysis without excessive fibrosis or granuloma formation, or fibrous extension into the lung or chest wall (Adler & Rappole 1967) and produces negligible loss of pulmonary function (Starkey 1964). It is non-toxic and treatment rarely has to be repeated. I have used iodized talc on a very large number of patients for 25 years and have seen no evidence of the development of mesothelioma of the pleura.

In the case of malignant pleural effusions talc or iodized talc creates pleural symphysis and so stops the reaccumulation of the effusion (Chambers 1958; Haupt et al. 1960; Camishion et al. 1962; Roche et al. 1963; Starkey 1964; Pearson & MacGregor 1966; Alder & Rappole 1967; Jones 1969). Talc is also successful in the treatment of chylothorax (Gingell 1965).

Various techniques for applying the talc in the treatment of malignant effusions have been proposed. A few surgeons perform thoracotomy through a short incision, break down all loculi, take biopsy specimens from the pleura, lung or nodes, remove restrictive pleura when necessary and then apply the talc (Haupt et al. 1960; Camishion et al. 1962;

Table II. Summary of results

Authority	*Technique*	*No. of patients*	*Successful control*	*Operative deaths*
Chambers (1958)	Single intercostal cannula	20	17	
Haupt et al. (1960)	Thoracotomy	19	19	
Camishion et al. (1962)	Thoracotomy	34	29	3
Roche et al. (1963)	Single intercostal	6	6	
Starkey (1964)	Thoracotomy	6	6	
Pearson and MacGregor (1966)	Thoracotomy Single intercostal cannula Two intercostal cannulas†	21 (23)*	17	1
Adler and Rappole (1967)	Single intercostal cannula	4	4	
Jones (1969)	Single intercostal cannula	21 (23)*	21	

* Numbers in parentheses indicate the number of effusions treated.

† Two intercostal cannulas were preferred to one and used in later cases.

Starkey 1964; Pearson & MacGregor 1966), by insufflation (Haupt et al. 1960) or as a cream made with saline (Camishion et al. 1962) or by rubbing on the powder with sponges on sponge holders (Starkey 1964).

The advantages claimed for thoracotomy are that operability of the growth can be assessed, biopsy can be performed, all loculi can be broken down, restrictive pleura can be removed and application of the talc to all pleural surfaces is assured. I consider that thoracotomy is unnecessary in the vast majority of cases and is too large an operation to be used routinely in patients with an inoperable tumour who are often in poor general condition and may not have long to live. It may be used occasionally in selected cases (Starkey 1964; Pearson & MacGregor 1966).

The results of talc pleurodesis obtained by other workers are similar to mine and are summarized in Table II.

CONCLUSIONS

1. Cancer of the lung is much more likely to give rise to a malignant pleural effusion in women than in men.
2. In the case of cancer of the lung adenocarcinomata are particularly liable to cause malignant pleural effusions.
3. Adenocarcinomata appear to have a special tendency to disseminate their cells into pleural effusions, whereas squamous cell tumours and sarcomas, other than the lympho-leukaemia group, have little tendency to do so. Oat cell tumours are intermediate in this respect.
4. The large majority of malignant pleural effusions in men are caused by cancer of the lung, whereas in women extrathoracic cancers are at least as frequent.
5. Bilateral malignant pleural effusions are more often caused by extrathoracic cancers than by cancer of the lung.
6. Pleural effusion in cancer patients may or may not be due directly to the tumour, and may or may not be due to malignant changes in the pleura. Non-malignant effusion may be caused by obstructive pneumonitis, pulmonary infarction or radiation injury of the lymphatic drainage.
7. Malignant effusions may nor may not be blood-stained, and they may or may not contain malignant cells, according to their cause and to the nature of the tumour.
8. Diagnosis can be made in a high percentage of cases by exfoliative cytology and tissue biopsy. It was established by these methods in 75% of patients in the present series.
9. In my opinion most malignant pleural effusions are due to lymphatic obstruction, a few are due to direct or metastatic involvement of the pleura and a very few may be due to superior vena caval obstruction. Pleural metastases may occur without effusions and effusions without metastases. The presence of pleural metastases does not exclude mediastinal lymphatic obstruction as the cause of the effusion.
10. Before treating a pleural effusion in a cancer patient, non-malignant causes should be corrected.
11. Malignant effusions which reaccumulate rapidly and embarrass respiration should be treated by intercostal talc pleurodesis using two cannulae, unless the disease is terminal. The effusion can be eliminated or controlled in nearly all patients by this technique,

whatever the cause, and wherever the primary tumour may be. Thoracotomy in association with talc is rarely required.

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ADRENAL INFARCTION: AN UNUSUAL COMPLICATION OF WEGNER'S GRANULOMATOSIS

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Summary

The case of a patient with Wegner's granulomatosis who died with haemorrhagic adrenal infarction is described. Thyroid involvement, another feature not previously reported in this disease, was also noted.

INTRODUCTION

Wegner's granulomatosis is a disease of unknown cause which Wegner (1936) described as a necrotizing granulomatous vasculitis involving the upper and lower respiratory tract associated with glomerulonephritis.

Renal failure was the commonest cause of death before the use of immunosuppressive drugs. We describe a patient who died with adrenal haemorrhage after an initially good response to cyclophosphamide.

Case Report

A 46-year-old ex-baker developed deafness in November 1976. Severe serous otitis media was diagnosed and myringotomy was performed.

In January 1977, while visiting Saudi Arabia, he was again seen in an ENT clinic because of bilateral otitis media. He was noted to have a cough and had lost 7 kg in weight. He smoked 30 cigarettes a day. The chest radiograph showed a lobulated opacity (6 × 11 cm) at the right apex and a 2.5 × 4.5 cm opacity at the left apex. Aspiration lung biopsy showed diffuse fibrosis, occasional foci of necrotic tissue and occasional focal areas of histiocytic proliferation. There was no evidence of malignancy.

He was started on antituberculosis therapy with isoniazid and ethambutol. He returned to the United Kingdom and was referred to Nevill Hall Hospital on 17 January 1977. His main complaint was of deafness and burning pain in both legs. He was cachetic with a continuous fever. He had also recently developed signs of irridocyclitis. The chest radiograph (Fig. 1) showed cavitation at the right apex, the left apical opacity remaining unchanged. Sputum examination showed no malignant cells or tubercle bacilli. Plasma viscosity was elevated to 2.17 cP (normal 1.5–1.72 cP). RA Latex was positive (1/320). Liver biopsy and sternal marrow biopsy were unhelpful.

The patient's condition became progressively worse, he developed large ulcers on the mucosa of the pharynx, mouth and tongue, and purpuric blisters on the extensor aspects of the elbows, fingers and right heel. Biopsy of the oral lesions showed a vasculitis mainly affecting the small arterioles, with mixed polymorphonuclear (including eosinophil) infiltrate in their walls.

A diagnosis of Wegner's granulomatosis was made. Treatment began with oral cyclophosphamide, 100 mg daily. There was rapid general improvement, subsidence of fever and healing of oral and cutaneous ulcers. The plasma viscosity returned to normal. The chest radiograph showed some diminution in the size of the apical opacities. White blood count and platelets were within normal limits.

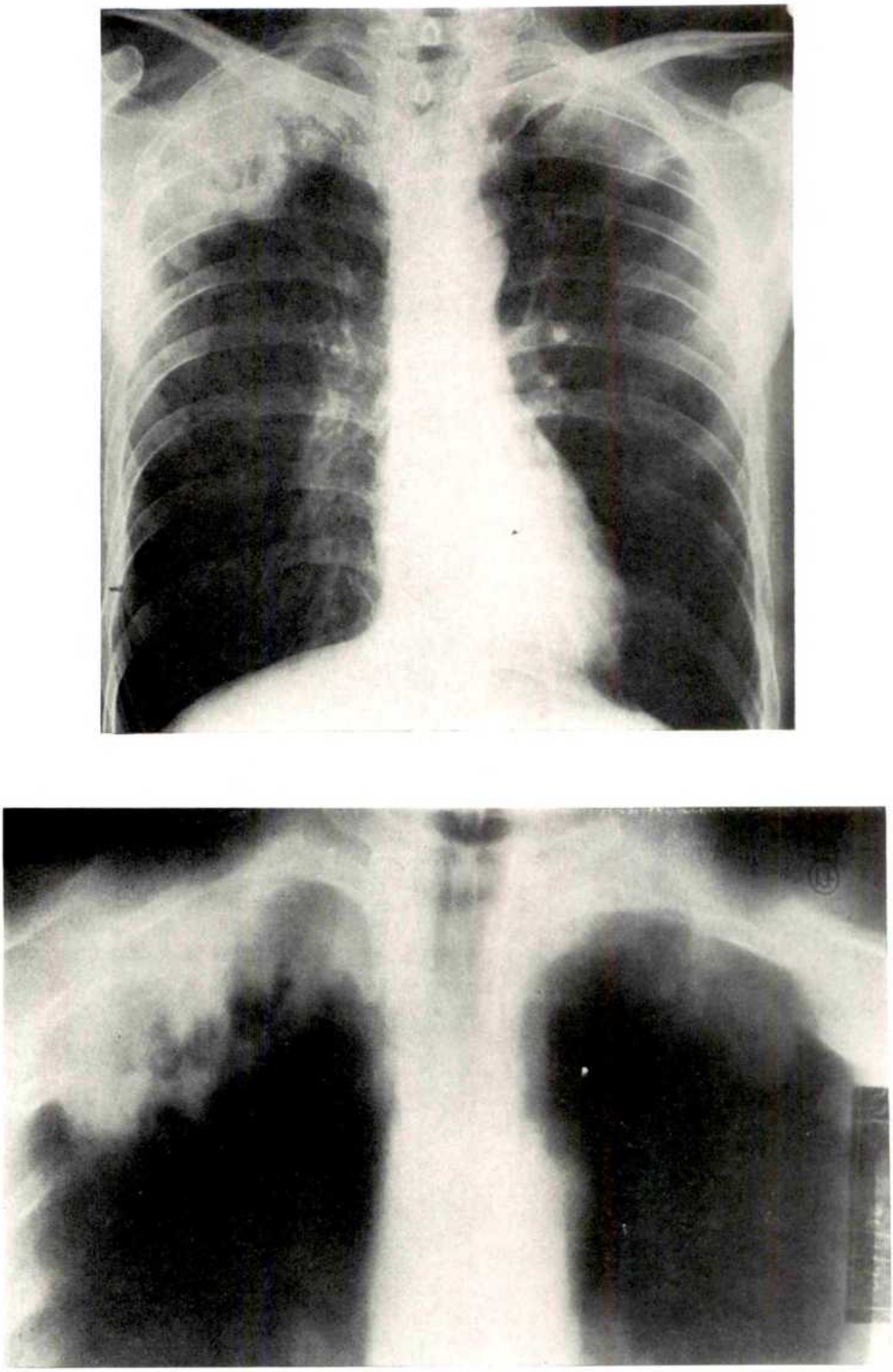

Fig. 1. Chest X-ray and tomogram showing cavitating apical opacities

After 11 days' therapy, the patient complained of pain in the right leg and within 15 minutes became collapsed and shocked. A presumptive diagnosis of pulmonary embolism was made. Despite intravenous heparin and hydrocortisone the patient died within three hours.

At autopsy there was no evidence of pulmonary embolism or peripheral venous thrombosis. In the right adrenal gland there was necrotizing arteritis and a haemorrhagic infarction and associated retroperitoneal haemorrhage. The thyroid gland also showed small infarcts. The histological findings in the apical lung lesions were consistent with Wegner's granulomatosis. The kidneys contained necrosis in the glomerular tufts. There was a large pale splenic infarct.

Discussion

This case demonstrates many of the typical manifestations described in Wegner's granulomatosis. Serous otitis media, cavitating lung lesions, iridocyclitis, oral and skin lesions are accepted features. This patient did not show any signs, in life, of the renal involvement which can be fatal.

We report this case in view of the involvement of the adrenal glands. This, like the thyroid disease also seen, has not previously been reported. Haemorrhagic infarction of the adrenal gland appears to have been the main terminal event. Cyclophosphamide was the drug chosen for treatment and corticosteroids were not used (except terminally), as a review of recent literature (Israel & Patchefsky 1971; Novack & Pearson 1971; Fauci & Wolff 1973) suggested that they have been unpredictable in effect and generally unhelpful. The initial response to cyclophosphamide in our patient was extremely encouraging, but as the terminal event may have been adrenal insufficiency it is possible that the addition of corticosteroids to his initial therapy could have prevented death. Assessment of adrenal function might have been a useful investigation in the management of this patient with Wegner's granulomatosis.

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HAEMOPTYSIS IN EOSINOPHILIC GRANULOMA

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Eosinophilic granuloma of bone may involve the lung in about 20% of cases (Lewis 1964); and may present in the lung without other organ involvement. Haemoptysis occurs in about 10% of cases for unknown reasons. I document here a case with typical presentation and course, but which was complicated by haemoptysis of increasing severity leading to death. The cause of haemoptysis was diagnosed at fibreoptic bronchoscopy.

Case Report

A white male presented at the age of 12 years with pain in the hip. A radiograph showed a bone cyst of the left innominate bone. This was subsequently explored, curetted, and filled with bone chips. He remained well until January 1960 when, at the age of 18 years, he left school to become apprenticed to a cabinet-maker. After working in the dusty upholstery department he became unwell with nocturnal sweating attacks and over a few weeks lost 3.5 kg (8 lb) in weight. He was admitted to the local hospital as he was found to have lymphadenopathy and splenomegaly. The blood film was normal and his chest radiograph was thought to be compatible with sarcoidosis. Liver biopsy was 'non-contributory' and lymph node biopsy showed 'reactive change only'. Serum and 24-hour urinary Ca^{2+} were normal and a Kveim test was reported as being negative. Mantoux testing was negative to 10 tuberculin units.

He was referred to Professor Scadding at the Brompton Hospital in 1961. The patient had no respiratory symptoms or abnormal physical signs. The chest radiograph showed a widespread reticular pattern. In view of the history of a bone cyst a preliminary diagnosis of eosinophilic granuloma was made and confirmed by reviewing the tissue obtained at the operation on the innominate bone. He remained well until August 1963 when he developed a spontaneous left pneumothorax. A rubber Malecot catheter was inserted in the second left interspace and 5 ml of 10% camphor oil injected down the tube into the pleural cavity. The tube was connected to an underwater seal allowing reinflation of the lung. After five days the tube was removed leaving a small pneumothorax, and after a further 17 days the patient was discharged with no residual air in the pleural space. He was admitted within two weeks with a recurrence of the left pneumothorax. An intercostal tube was inserted and the lung re-expanded, allowing removal of the tube after three days. Later that day his condition suddenly deteriorated with recurrence of the pneumothorax and extensive subcutaneous emphysema. He was taken to theatre and the chest opened through a left posterolateral incision. The visceral pleura was thickened and although no subpleural bullae were seen, large cystic spaces were felt deeper in the lung substance. A small hole was present in the upper lobe and looked as if it had been caused by an instrument. This was doubly ligated and a parietal pleurectomy carried out. The postoperative course was uneventful and he was discharged.

His pulmonary function deteriorated little after the pleurectomy but in view of any possible improvement with corticosteroids he was given prednisone 30 mg daily for one week and then 20 mg daily for a further three weeks. After this there was an improvement in well-being and an increase in the gas transfer factor (Table I). Prednisone was continued at a dose of 15 mg daily and gradually reduced until by May 1965 he was taking 7.5 mg daily (Fig. 1).

Table I. Results of lung function tests in the early stages of the disease

Date	*Age*	FEV_1 (ml)	FVC (ml)	*PEFR* (litres/min)	*DLCO** (ml/min/mmHg)
March 1961	18	2400	3300	500	9.2
Nov. 1962	20	2300	2700	—	6.6
Nov. 1963	21	2000	2700	330	7.8
Dec. 1963	21	2150	2950	340	11.2
May 1964	22			350	10.0

* Steady state at rest.

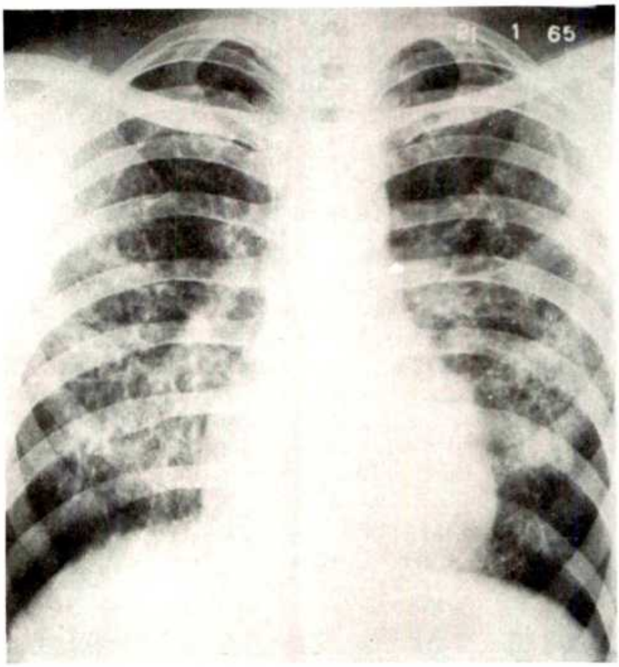

Fig. 1. Chest radiograph in 1965

In July 1965 he was admitted with a one-day history of severe shortness of breath and a little sputum. He had had a dry cough for many years and had been smoking 30 cigarettes daily. During this admission no new features were found and his symptoms resolved after a course of tetracycline. After this admission he stopped smoking and by September 1966 was 'very well' and able to play rugby and squash.

He was admitted again in January 1967 because of breathlessness following a cold. He was producing 50 ml of sputum daily and *Haemophilus influenzae* was isolated from it on this admission. His symptoms gradually resolved following treatment with ampicillin. At routine follow up in May 1967 he gave a history of left-sided chest pain and cough for one week which had improved spontaneously. The chest radiograph at this time showed a marked increase in the left mid-zone shadowing (Fig. 2). Sputum was purulent and he was again given ampicillin. He started smoking again and against advice, continued to smoke over the next few years. There was intermittent production of mucopurulent sputum but the patient remained well until June 1972 when he coughed up about

20 ml of blood over a two-day period. His chest radiograph was unchanged and his symptoms did not recur after a course of ampicillin.

In June 1975 he was admitted because of four or five haemoptyses, each of 100–150 ml of bright red blood, over a 10-day period. Apart from this he had been well, was able to carry out a normal life as an antique dealer and could carry heavy furniture up and down stairs. He was producing about 10 ml of mucopurulent sputum daily. On examination he was sun-tanned and looked well. There was mild clubbing of the fingers. The chest was flattened in the left upper zone anteriorly where movements, tactile vocal fremitus, percussion note and breath sounds were all reduced. Late inspiratory crackles were heard over the left lung. The spleen was not palpable but could be percussed easily, and the scar over the left hip was noted. An ejection click was heard at the left sternal edge and the pulmonary component of the second heart sound was accentuated. All therapy (including corticosteroids) had been stopped in 1966.

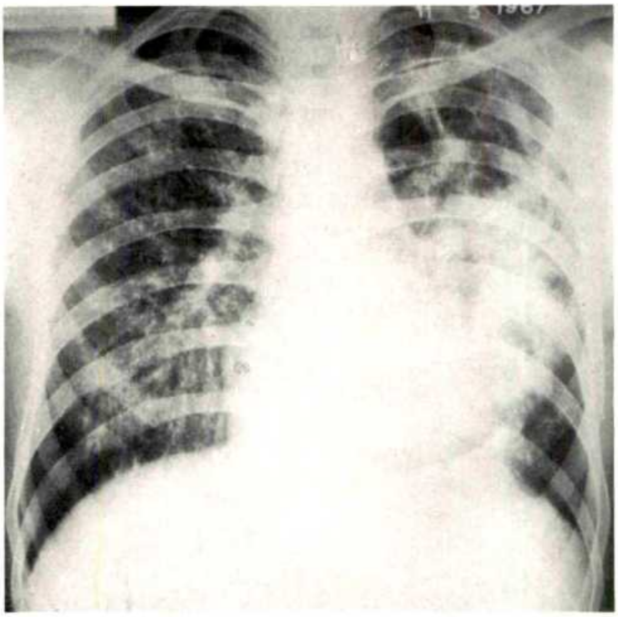

Fig. 2. Chest radiograph in 1967, showing left mid-zone shadowing

Blood and serologial examinations were as follows: haemoglobin 11.7 g/100 ml; white cell count 10 800/mm^3; prothrombin time 14 sec (control 12 sec); electrolytes and urea normal; liver function tests normal. Immunoglobulins were IgG 1327 mg/100 ml; IgA 350 mg/100 ml; and IgM 156 mg/100 ml. Sputum was mucopurulent and contained many white cells with 10% eosinophils. *Haemophilus influenzae* was again isolated. ECG showed right axis deviation, a feature not noted in 1965. Mantoux testing was negative at 1 T.U. but an extract of *Candida albicans* produced 8 mm of induration after 48 hours. Respiratory function tests are listed in Table II and the chest radiograph is shown in Fig. 3.

On the second day of admission he coughed up about 600 ml of blood. He was treated conservatively and by the following morning his haemoglobin had fallen to 10.1 g/100 ml. The chest radiograph was unchanged and fibreoptic bronchoscopy was carried out.

At bronchoscopy, a little old blood was seen in the right main bronchus just below the upper lobe orifice; otherwise this side was normal. On the left side the major bronchi and segments were all inflammed. In a division of the anterior segment of the left upper lobe some material was seen which had the appearance of mycelium. This was biopsied without producing any bleeding. No active bleeding was seen.

Table II. Respiratory function tests on admission in 1975*

	Predicted value	*Observed value*	*After bronchodilator*
FEV_1 (ml)	4120	1460	1900
FVC (ml)	5120	2350	2860
FEV_1/FVC (%)	80.5	62	66
VC (ml)	5120	2500	
FRC (ml)	3870	3610	
TLC (ml)	7050	5460	
RV/TLC (%)	27	54	
Raw (cm H_2O/litre/sec)		2.6	
DLCO (ml/min/mmHg)	34.0	12.6	
KCO	5.3	3.3	

* Spirometry was recorded on a Vitalograph dry spirometer and lung volumes in a body plethysmograph. Gas transfer (DLCO) was measured with a single breath technique.

Fifteen hours after bronchoscopy, during the night, he was found coughing up a large amount of blood. He collapsed and could not be resuscitated. Throughout resuscitation his ECG showed asystole with occasional ventricular beats but no cardiac output occured.

The biopsy obtained at operation was found to consist of pure mycelium (Fig. 4) and pieces sent to the microbiology laboratory gave a pure growth of *Aspergillus fumigatus*. Blood taken in life was examined for fungal precipitins. These were found to be present to *Aspergillus fumigatus*.

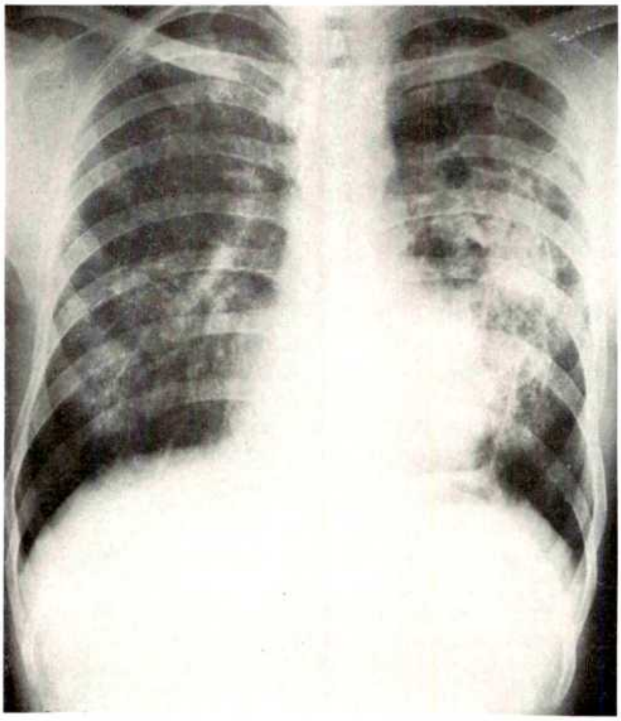

Fig. 3. Chest radiograph on admission in 1975

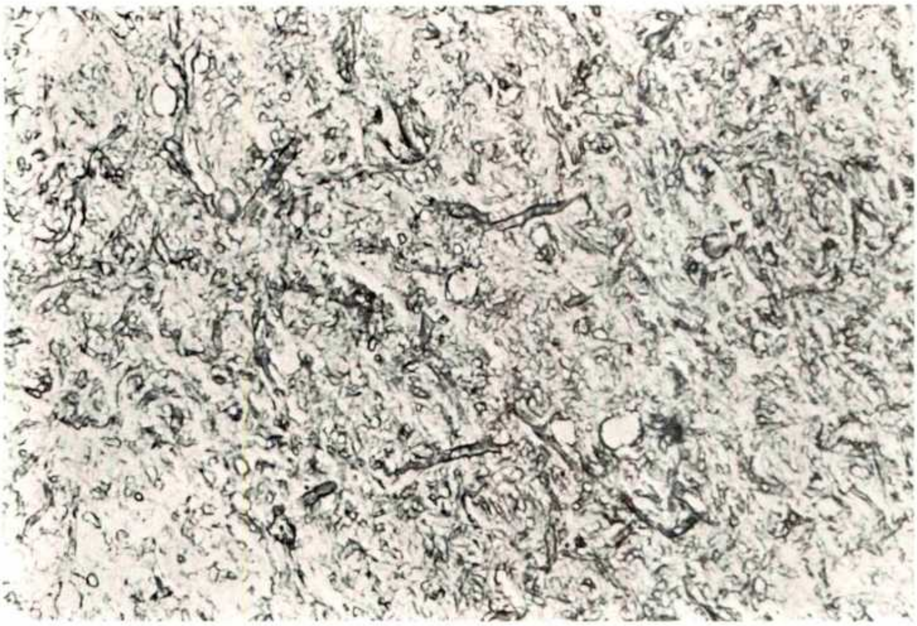

Fig. 4. Biopsy of endobronchial mycelium. Grocott × 300

At post-mortem examination the right pleural cavity was obliterated by adhesions and the left pleural cavity completely obliterated by the previous pleurectomy. The trachea and major bronchi on both sides were filled with blood. The cut surface of the right lung showed diffuse fibrosis and emphysema in the upper lobe with a cavity about 2 cm in diameter, containing a mycetoma. The left upper lobe showed gross diffuse fibrosis with emphysema and a peripheral cavity about 4 cm in diameter containing a mycetoma. This cavity was open to a bronchus. Both lower lobes were consolidated by aspirated blood and were also fibrous and emphysematous. The heart was normal in size but the right ventricular wall approximated in size to that of the left (1.2 cm). The spleen was slightly enlarged. *Aspergillus fumigatus* was isolated from swabs taken from both mycetoma cavities.

Microscopy of the lung showed diffuse fibrosis; eosinophilic granuloma lesions were not apparent. Section of the larger mycetoma cavity showed it to be lined with highly vascular granulation tissue.

DISCUSSION

This patient presented with eosinophilic granuloma of bone and subsequently developed pulmonary manifestation of the disease. His progress was complicated by pneumothorax, a feature found in 24% of cases with pulmonary involvement (Lewis 1964). Although mycetoma has been reported with other types of pulmonary fibrosis it has not, as far as I am aware, been reported with eosinophilic granuloma. We were able to diagnose patient's left-sided mycetoma at fibreoptic bronchoscopy. The right-sided mycetoma was not diagnosed in life and, even in retrospect, was invisible on the chest radiograph.

The presence of a mycetoma should be suspected in any patient with diffuse pulmonary fibrosis and haemoptysis even if the radiographic appearances are unremarkable. The measurement of fungal precipitins in the serum would help confirm the diagnosis. A number of techniques might help find the site of the lesion. Whole-lung tomography would be the simplest investigation possibly followed by the radio-isotope method described by Rawal and Adiseshan (1976). Fibreoptic bronchoscopy might be useful in those patients with endobronchial mycelium but would be most useful in tracing the source of blood in patients actively bleeding (Smiddy & Elliott 1973). If pulmonary function was reasonably maintained the early diagnosis of this complication might allow operative intervention with the prevention of the fatal haemoptysis suffered by this patient.

ACKNOWLEDGEMENTS

I am indebted to Dr Peter Cole for permission to publish this report and to Sister Anne Newport for her invaluable help in the bronchoscopy room. Dr K. F. W. Hinson carried out the post-mortem examination and interpreted the histology.

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TUBERCULOSIS OF THE THYROID: TWO CASE REPORTS

PETER BARNES AND ROBERT WEATHERSTONE

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Summary

Tuberculosis of the thyroid gland occurs only rarely. Since extrapulmonary tuberculosis is now seen relatively more frequently the existence of this condition should be recognized. The cases of two patients with tuberculosis involving the thyroid are presented. The first, an Asian immigrant, presented with a painless goitre with no evidence of tuberculosis elsewhere. The second was an English woman who presented with hypothyroidism due to destruction of the thyroid by tuberculosis, and who subsequently died with disseminated tuberculosis; this is the only case to report the association between myxoedema and tuberculous thyroiditis. Other manifestations of thyroid tuberculosis and the pathological types are discussed.

INTRODUCTION

Tuberculosis of the thyroid gland is extremely uncommon with very few cases reported in recent years. Symptom-free thyroid involvement may occur as part of generalized miliary spread or, more rarely, diffuse or localized swelling of the gland may dominate the clinical picture. In all of the recent case reports the patients have been clinically and biochemically euthyroid..

Two patients are described. The first presented with a goitre. The second with myxoedema, which has never previously been reported as a complication of tuberculosis.

Case Reports

Case 1

A 29-year-old Goan Indian who had lived in England for two years presented in July 1977 with a painless swelling of the neck which had been present for at least six months. For three months he had complained of a persistent non-productive cough but there were no symptoms of stridor, dysphagia or hoarseness. He had lost 12 kg in weight over the same time but there were no other constitutional symptoms or other symptoms of thyroid dysfunction. There was no previous or family history of tuberculosis or thyroid disease.

Examination revealed a fit-looking man with low-grade pyrexia. The thyroid gland was enlarged (the right lobe more than the left), nodular and firm, with an apparent retrosternal extension. The gland was mobile on swallowing and no bruit was heard. No cervical lymph nodes were palpable and the overlying skin was normal. He was clinically euthyroid, the chest was clear and the vocal cords moved normally at laryngoscopy.

Investigations revealed a haemoglobin of 12.2 g/dl, white cell count of 8.8×10^9/litre with a normal differential and an ESR of 67 mm/hour (Westergren). Thyroid function tests showed serum thyroxine 94 nmol/litre, tri-iodothyronine 1.3 nmol/litre and thyroid stimulating hormone

28 mU/litre (normal range 0–4 mU/litre). Thyroid autoantibodies were not present. A Mantoux test using 1 T.U. gave a strongly positive reaction (1.7 cm induration). The chest radiograph showed a central superior mediastinal mass; the lung fields were clear. Tomography revealed a right paratracheal mass probably representing lymph node enlargement, but no tracheal compression. A thyroid scan showed diffuse thyroid enlargement with markedly reduced and patchy uptake of isotope and the ^{131}I uptake at 24 hours was 2.5% (normal range 20–55% of total dose). There was no evidence of tuberculosis elsewhere; a lumbar spine radiograph and intravenous pyelography were normal, and three early morning urine specimens failed to grow tubercle bacilli on culture.

At operation (Mr A. G. A. Cowie) the thyroid was diffusely swollen and hard, with multiple abscess cavities within its substance. Microscopy of aspirated pus revealed numerous acid-fast bacilli, shown to be *Mycobacterium tuberculosis* on culture, which was fully susceptible to standard antituberculous drugs. Histology of a thyroid biopsy showed numerous caseating giant cell granulomata characteristic of tuberculosis interspersed with normal thyroid tissue (Fig. 1).

Administration of rifampicin, ethambutol and isoniazid was followed by gradual resolution of the thyroid swelling. The patient was discharged from hospial 1 month after admission.

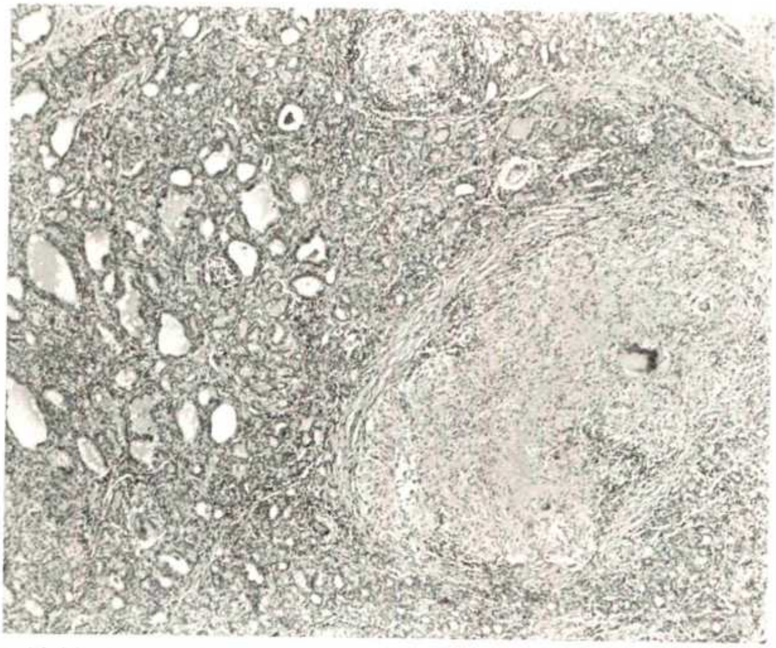

Fig. 1. Thyroid biopsy showing a caseating granuloma surrounded by normal thyroid tissue. H & E ×80

Case 2

A 79-year-old English woman, who had lived all her life in London, presented in February 1971 with a two-month history of progressive lethargy and hoarseness of the voice. She had no respiratory symptoms or past history of tuberculosis or thyroid disease. On examination at that time she was afebrile and appeared pale and obese, with a myxoedematous facies and dry skin. There was sinus bradycardia and the tendon reflexes were slowly relaxing. The thyroid was impalpable. A clinical diagnosis of hypothyroidism was confirmed biochemically by a protein bound iodine (PBI) of 2.4 μg/dl (normal range 3.7–8.1 μg/dl). Other investigations included a haemoglobin of 11.4 g/dl with a normochromic normocytic picture, white cell count of 4.5×10^9/litre and ESR of 98 mm in 1 hour. A chest radiograph showed patchy consolidation in the right lower lobe, and she was given a course of ampicillin for a presumed bacterial chest infection. Treatment was started with 1-thyroxine 0.05 mg daily.

She was readmitted six months later with continuing lethargy and recent weight loss. At that time she was febrile with a temperature of 38 °C and there were signs of bilateral bronchopneumonia, confirmed radiologically. The PBI on this admission was 4.0 μg/dl when she was taking 1-thyroxine 0.15 mg daily. The haemoglobin was now 9.6 g/dl, white cell count 4.5 × 10^9/litre and the ESR 83 mm/hour. No acid-fast bacilli were demonstrated on direct microscopy of sputum, but culture subsequently yielded *Mycobacterium tuberculosis* susceptible to all standard antituberculous drugs.

Despite antibiotics her condition deteriorated and she died two weeks after admission. At autopsy she had diffuse tuberculous bronchopneumonia with caseating granulomata and many acid-fast bacilli in the liver and mediastinal lymph nodes. The thyroid gland was completely replaced by yellowish necrotic material, shown histologically to be caseating granulomata with many acid-fast bacilli, and with no normal thyroid tissue preserved.

DISCUSSION

In the nineteenth century it was authoritatively suggested that tuberculosis never involved the thyroid gland (Rokitansky 1859), and that there was some antagonistic action between a goitre and tuberculosis so that the presence of a thyroid swelling was proof that the patient did not have tuberculosis (Virchow 1864). Lebert (1862) reported the first case of tuberculous thyroid involvement in a patient with disseminated miliary tuberculosis and Chiari (1878) described seven cases of microscopic involvement of the thyroid in 100 autopsies of patients who had died from disseminated tuberculosis. Sporadic reports followed in which there was miliary spread to the thyroid but no abnormality of the thyroid was suspected clinically. Bruns in 1893 described the first case of tuberculous thyroiditis diagnosed in life in a middle-aged woman with a rapidly enlarging goitre who had cervical lymphadenopathy but no evidence of pulmonary tuberculosis. The first report of successful drainage of a tuberculous thyroid abscess was by Schwartz in 1894. Five cases of thyroid tuberculosis were described by Coller and Huggins (1926) in a series of 1200 cases of thyroid disease operated on between 1921 and 1926; all of these, however, showed miliary tuberculosis occurring in pre-existing goitres. Rankin and Graham (1932) studied a large series of 20 758 partial thyroidectomy specimens from the Mayo Clinic between 1920 and 1931 and diagnosed tuberculosis in only 21 cases, an incidence of 0.1%. A similar incidence was confirmed more recently by Levitt (1952) who found only two cases of tuberculosis among 2114 consecutive thyroidectomy specimens. The rarity of the condition in recent years is emphasized by Bolis (1970) who found two cases of fibrocaseous tuberculosis in 74 393 consecutive thyroid biopsies in an Italian centre. Only isolated clinical case reports are to be found in the recent literature (Klassen & Curtis 1945; Goldfarb et al. 1965; Crompton & Cameron 1969; Johnson et al. 1973).

Tuberculosis may involve the thyroid gland in two main forms. The more common of these is miliary spread to the thyroid as part of generalized dissemination but this form has never been shown to give rise to clinical thyroid disease (Rankin & Graham 1932). Occasionally miliary spread may occur in pre-existing thyroid enlargement (Coller & Huggins 1926).

Less commonly focal or caseous tuberculosis of the thyroid may occur, presenting as a localized swelling mimicking carcinoma (Crompton & Cameron 1969; Hajjar & Salti

1973), as a cold abscess appearing superficially (Rankin & Graham 1932), very rarely as an acute abscess (Goldfarb et al. 1965; Johnson et al. 1973), or as diffuse thyroid enlargement illustrated by Case 1. Fibrosis and adherence to adjacent structures may occasionally give rise to pressure symptoms (Hazard 1955) with dyspnoea, dysphagia or recurrent laryngeal nerve palsy (Joll 1932). Microscopically there is destruction of thyroid tissue with caseating tuberculous granulomata. It may be distinguished from sarcoidosis (Karlish & MacGregor 1970) and subacute (giant cell) thyroiditis (Greene 1971) by the presence of caseation and by the demonstration of acid-fast bacilli.

Chronic fibrosis of the thyroid has been described in association with tuberculosis, particularly by European authors (Roger & Garnier 1900; Andretta 1968) although the exact aetiological relationship of sclerosing thyroiditis to tuberculosis remains in doubt.

Disorders of thyroid function have seldom been described in association with tuberculous thyroiditis. Mosiman (1917) recorded nine cases in which seven were said to be thyrotoxic on clinical grounds, although no biochemical confirmation was possible. It seems likely that the weight loss and elevated basal metabolic rate described in these cases may have been explained by the underlying tuberculosis. Indeed it has been suggested that thyrotoxicosis affords some protection against infection by *M. tuberculosis* (Joll 1932). Hypothyroidism as a result of progressive thyroid destruction may be expected to occur but in the few cases in which indices of thyroid function have been measured biochemically normal values have been obtained. In Case 1, with diffuse thyroid enlargement, the serum thyroxine and tri-iodothyronine levels were within normal limits, but the TSH level was elevated, indicating early hypothyroidism. Case 2, however, is the only recorded case to have presented with myxoedema resulting from thyroid destruction by tuberculosis.

Diagnosis of tuberculous involvement of the thyroid is not difficult to make if its possibility is appreciated. Seed (1939) required three conditions to be met before a diagnosis of tuberculous thyroiditis could be made. These were the finding of acid-fast bacilli within the thyroid, a necrotic or abscessed gland, and the demonstration of a definite tuberculous focus outside the thyroid. Histological and bacteriological confirmation is adequate to make the diagnosis, and fulfilment of the third criterion is not essential; in Case 1, there was no proven focus of tuberculosis outside the thyroid.

The treatment of tuberculosis with *para*-aminosalicylic acid (PAS) may itself produce a goitre (Clausen & Kjerulf-Jensen 1951) and over 200 such cases have now been described. PAS is thought to have an action similar to propyl thiouracil and there is complete resolution of the goitre when the drug is discontinued (Munkner 1969).

Extrapulmonary tuberculosis occurs more frequently amongst Asians (Report of the Research Committee of the British Tuberculosis Association 1966) and as tuberculosis is more common in the immigrant population it is important to be aware of the unusual ways in which it may present as early treatment is important.

ACKNOWLEDGEMENTS

We would like to thank Dr P. J. D. Heaf and Dr J. F. Stokes for allowing us to report cases under their care, Dr S. Lucas for advice about the pathology and Miss R. Manley-Cooper for secretarial assistance.

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Br. J. Dis. Chest (1979) *73*, 192

UNUSUAL COURSE OF BERYLLIUM LUNG DISEASE

P. J. Rees*

The London Chest Hospital

Summary

The cases of two patients with beryllium disease of the lung are reported in which acute exposure produced immediate symptoms and progressed to chronic disease with no latent period.

INTRODUCTION

Acute lung disease after exposure to beryllium or its salts was first described in Germany in 1933 (Weber & Englehardt 1933), and the chronic form of the disease with a delayed onset was recognized in the United States in 1946 (Hardy & Tabershaw 1946). Over 800 cases of lung disease associated with beryllium exposure have now been recorded in the United States Beryllium Case Registry (Hasan & Kazemi 1974) and over 40 cases have been reported in the British literature. Until 1967 acute disease progressing to chronic disease after a variable time interval was recorded in only 6% of cases (Hardy et al. 1967). Only one case of acute disease has been recorded in the British literature (Royston 1949) and in this case symptoms and radiological changes resolved on removal from exposure and at one year from the onset there was no evidence of disease.

The cases of two patients reported here appear to present in a different way. Both had long worked in the beryllium industry and had no respiratory symptoms before their acute exposure. Both were briefly exposed to a large dose of beryllium fume after which they complained of fairly severe respiratory symptoms, and respiratory symptoms have continued since exposure. Lung biopsies showed histological changes typical of chronic beryllium disease (Freiman & Hardy 1970).

Case Reports

Case 1

A man aged 47 years presented in September 1971. Since 1961 he had worked in a factory where beryllium was used and since 1966 his job had involved melting beryllium. In September 1971 he was exposed to a large dose of beryllium fume because a batch for melting had been wrongly labelled. He felt unwell and complained of a headache, nausea and cough from the time of the acute exposure. Two to three weeks later he complained of lassitude and dyspnoea and still complains of dyspnoea on exertion. He had smoked 25 cigarettes per day until 1965, but none since.

In February 1972 there was no clubbing of the fingers. A few late inspiratory crackles were heard on auscultation of the chest. Investigations showed a negative Mantoux test at strength

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1 in 100. Kveim test was negative and beryllium patch test was positive. The chest radiograph showed extensive fine nodular shadowing with enlargement of hilar lymph nodes. A chest radiograph in 1970 had shown no changes consistent with beryllium lung disease. The respiratory function tests (Table I) in 1975 showed a considerable decrease in transfer factor with no decrease in vital capacity.

A drill biopsy of his lung (Dr S. J. Steel) in February 1972 showed many non-caseating granulomata with epithelial and giant cells surrounded by a zone of lymphocytes, some fine fibrosis was present (Dr B. Heard). He was given corticosteroids in March 1972 which have been continued.

An in vitro test of beryllium sensitivity estimating the release of migration inhibitory factor produced an equivocal result at a time when the patient was taking corticosterioids.

Table I. Pulmonary function tests

	Case 1		*Case 2*	
	Predicted	Nov. 75	Predicted	July 75
Vital capacity (litres	4.1	4.3	4.8	4.5
FEV_1 (litres)	3.0	3.4	3.6	2.6
Forced expiratory ratio (%)	70–80	83	70–80	61
Transfer factor (ml CO/min/mmHg)	25	17	31	24

Case 2

A man aged 44 years presented in October 1973. For several years he had worked in a factory using beryllium. In October 1973 he was accidentally exposed to a high concentration of beryllium fume after a breakdown in a furnace extraction process. Immediately after exposure his lips felt sticky, he complained of a cough and an hour later he felt wheezy. He has complained of a persistent cough and of shortness of breath since that time. He has never been a smoker and has no relevant family history or previous medical history. He is allergic to penicillin, plaster and iodine.

There was no clubbing of the fingers. Auscultation revealed widespread late inspiratory crackles. Mantoux test 1 in 100 was negative and the Kveim test was negative. A beryllium patch test produced a severe local reaction with blistering on the forearm. The chest radiograph showed widespread nodular shadowing in both lung fields and probable hilar gland enlargement. In July 1974 administration of corticosteroids was started. Respiratory function tests (Table I) in 1975 showed decrease in transfer factor with only slight decrease in vital capacity.

A specimen from a trephine biopsy of the lung (Dr S. J. Steel) in October 1974 showed several granulomata with central histiocytes, a surrounding thin band of collagenous tissue and a mantle of lymphocytes. There were occasional giant cells and one asteroid body was seen (Dr B. Heard). The migration inhibitory factor estimation was negative.

DISCUSSION

These two cases appear to represent an unusual course of beryllium lung disease. The patient's condition progressed from acute to chronic beryllium lung disease after acute exposure with no latent period. Both patients had worked in the beryllium industry for a number of years and it is conceivable that they had beryllium lung disease before acute exposure. Thus the acute disorder may have been superimposed on a symptom-free chronic disorder. Neither patient had respiratory symptoms before the exposure, and in the first patient the chest radiograph one year before exposure showed no evidence of beryllium lung disease.

The second case illustrates one of the dangers of the beryllium patch test. The cutaneous reaction to the application of beryllium sulphate was unpleasantly severe. There is one report of the exacerbation of lung disease following a beryllium patch test (Sneddon 1955). It is possible that the acute exposure in these two cases acted in a similar manner. The other theoretical danger is that the patch test may sensitize patients who do not have beryllium disease, thus increasing the risk of future exposure.

The immunological tests appear to offer the best hope of a diagnostic test. Neither of these patients had a positive response with the migration inhibitory factor technique carried out in Dr Jones-Williams' laboratory, which appears to be a common negative finding in patients taking corticosteroids (Jones-Williams 1972). Using a morphological counting technique of blast transformation on exposure of lymphocytes to beryllium sulphate in tissue culture, Deodhar et al. (1973) showed a positive response in 21 out of 35 patients on treatment with corticosteroids for chronic beryllium disease. Only one of 64 controls, including 30 unaffected beryllium workers, had a positive response.

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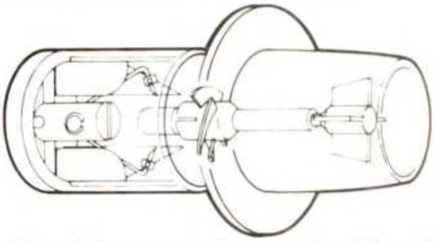

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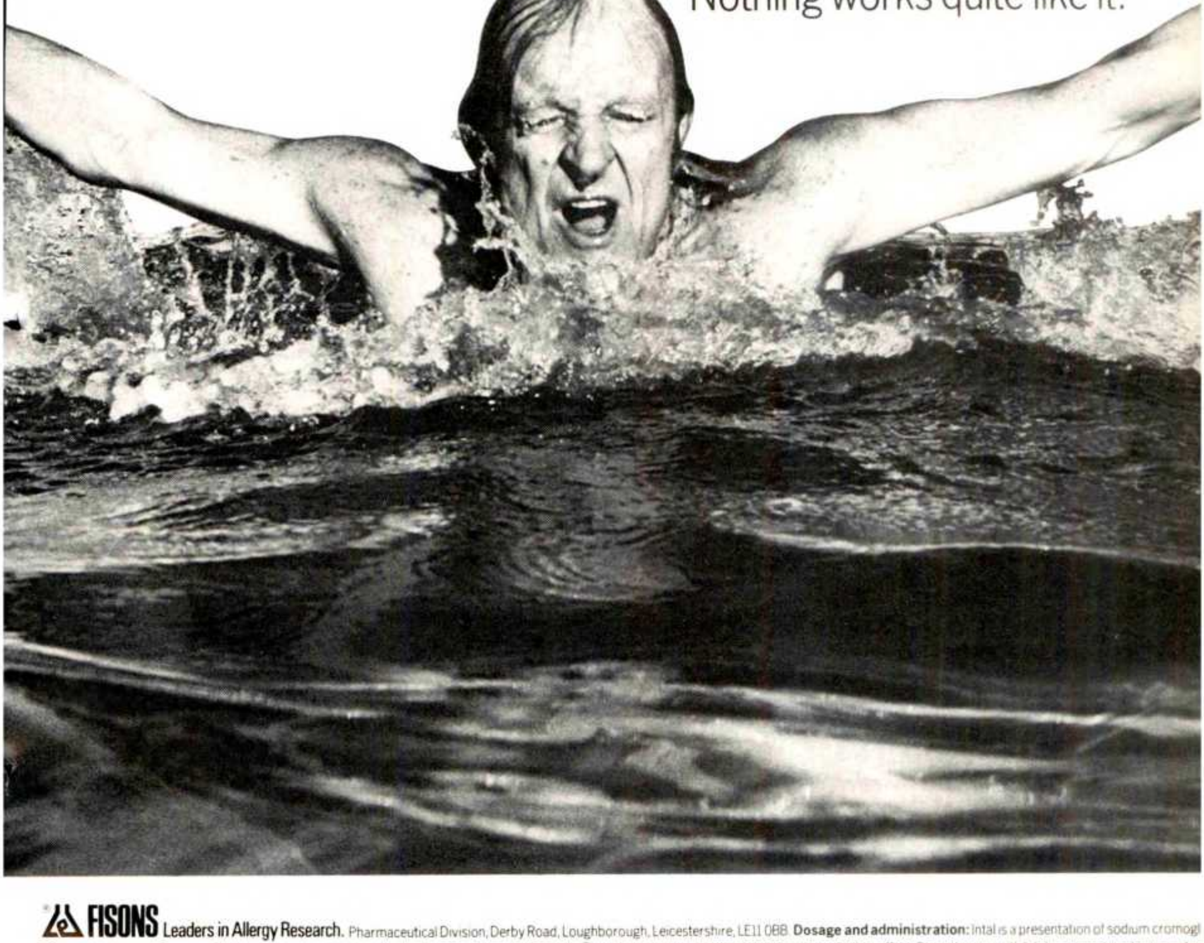

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Br. J. Dis. Chest (1979) 73, 195

PROGRESSIVE PLEURAL THICKENING DURING OXPRENOLOL THERAPY

R. L. PAGE*

Senior Medical Registrar, Department of Medicine, Ipswich Hospitals, Suffolk

Summary

A case of progressive pleural thickening developing during treatment with oxprenolol is described and the possible association between the two is discussed.

Case Report

A 31-year-old previously well man presented in December 1975 with headaches, was found to be hypertensive (blood pressure 200/130 mmHg) and was treated with oxprenolol (80 mg twice a day), cyclopenthiazide-K (0.25 mg daily) and diazepam (2 mg twice a day). Routine investigations including a chest X-ray were normal. In March 1976 he was admitted to hospital with the physical and radiological signs of an acute right lower lobe pneumonia (Fig. 1). The pneumonia resolved rapidly after a course of cephaloridine and he was discharged from hospital on his usual hypertensive regimen. When seen one month later he was feeling well and his chest X-ray was normal apart from blunting of the right costophrenic angle (Fig. 2). In order to achieve satisfactory blood pressure control the dose of oxprenolol was progressively increased to 120 mg four times a day over the course of the next year and bethanidine sulphate (10 mg three times a day) was added in June 1976. Both agents were eventually stopped in August 1977 and replaced by propranolol (80 mg three times a day) which he continued to take until May 1978, with satisfactory blood pressure control. Apart from experiencing slight discomfort in the right lower chest and latterly developing some exertional dyspnoea, he has remained well over this period and in particular has had no arthalgia, skin rashes, ocular symptoms or pyrexia. However, over the course of the past two years chest X-rays have shown progressive thickening of the pleura on the right (Fig. 3). Careful questioning and a search through his practitioner's records has confirmed that he has never had a chemical pleurodesis or chest trauma, nor has he been knowingly exposed to asbestos or other fibrogenic dusts or received methysergide or practolol. Repeated estimations of erythrocyte sedimentation rate, white cell count, rheumatoid factor, protein electrophoresis and autoantibodies have all been normal. In March 1978 a closed pleural biopsy was performed using an Abram's needle and it was noted that the pleura felt thickened and that there was no pleural effusion. Histological examination showed the pleura to be composed of dense fibrous tissue with areas of hyperplastic mesothelial cells. There was no significant inflammatory cell infiltrate and no evidence of malignancy.

DISCUSSION

Fibrous thickening of the pleura is a well recognized sequel to tuberculous pleural effusions and empyemas, post-pneumonic effusions and empyemas, haemothorax and the inhalation of asbestos, talc and possibly other fibrogenic dusts (Hourihane et al.

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* Present appointment: Senior Medical Registrar, Addenbrooke's Hospital, Cambridge.

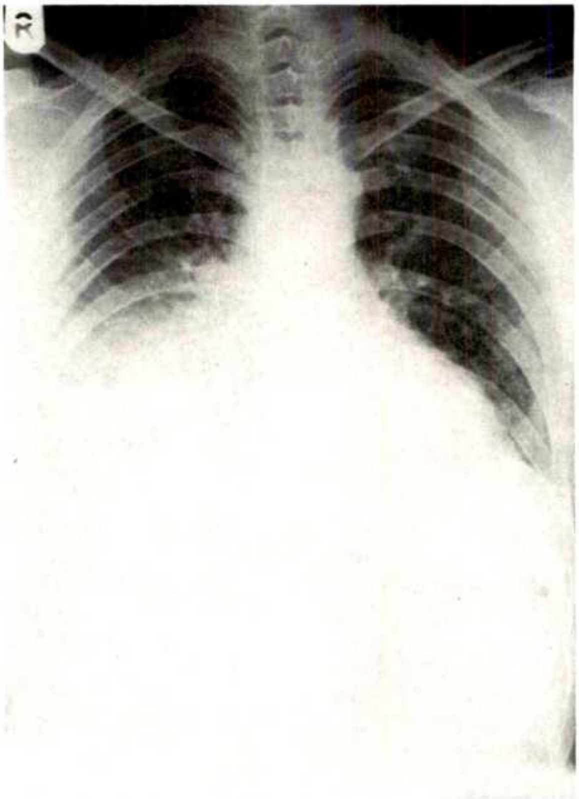

Fig. 1. Posteroanterior chest X-ray (March 1976) during admission with right lower lobe pneumonia

1966; Ochs & Smith 1976) and has also been associated with rheumatoid arthritis (Walker & Wright 1968; Jones 1978), scleroderma (Fraser & Paré 1978), methysergide therapy (Hindle et al. 1970) and practolol therapy (Dyer & Varley 1975; Fleming & Hickling 1975; Marshall et al. 1977).

Many of these causes can readily be excluded in this case but certain of them require further consideration. The right lower lobe pneumonia would superficially seem to be a candidate, but there are many features against such an association. Clinically, the pneumonia resolved rapidly, leaving only blunting of the costophrenic angle on an X-ray taken a few weeks later at a time when the patient was feeling well. Thereafter there were no stigmata of a continuing infective process, there being no fever, sweats or leucocytosis and when the pleura was biopsied there was no pleural effusion or evidence of inflammatory infiltrate in the pleura. In addition post-infective pleural fibrosis is not usually progressive but remains unchanged for many years (Fraser & Paré 1970). Many patients with asbestos-induced pleural fibrosis give no history of exposure (Kiviluoto 1960) but the unilateral disease, rapid progression, lack of calcification despite extensive involvement and absence of asbestos bodies in the pleural biopsy make this an unlikely cause.

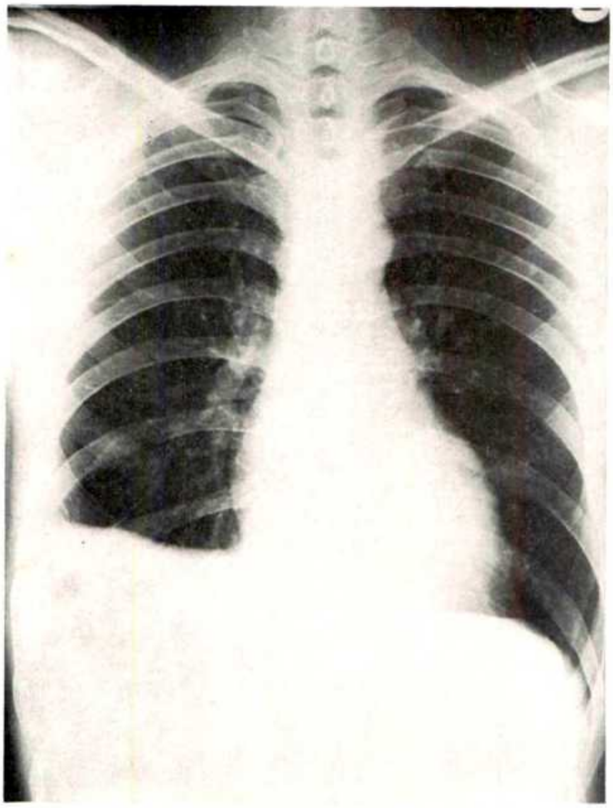

Fig. 2. Posteroanterior chest X-ray (May 1976) six weeks after right lower lobe pneumonia

Proving cause and effect with drug-induced disease is often difficult and relies on much circumstantial evidence. However, practolol-induced pleural disease is now well recognized and there are similarities between this case and those described by Marshall et al. (1977). Of their six cases, four had no evidence of pleural effusion and the process was unilateral in one. In each case pleural thickening progressed after cessation of practolol therapy. Oculocutaneous reactions (Cumberbatch 1974; Hudson & Finnis 1975; Holt & Waddington 1975; Knapp & Galloway, 1975) and fibrinous peritonitis (Kennedy & Ducrow 1977), similar to those associated with practolol therapy, have been reported with oxprenolol therapy and it is therefore suggested that oxprenolol may be responsible for the progressive pleural thickening described in this case and that further studies are warranted.

ACKNOWLEDGEMENTS

I thank Dr C. J. Stewart for allowing me to report this case and Dr R. C. G. Rowe for performing the histological studies.

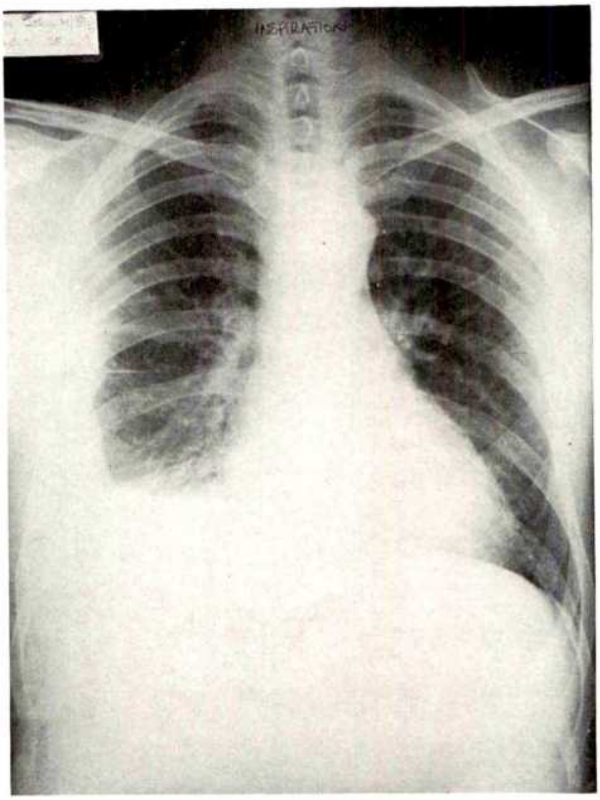

Fig. 3. Posteroanterior chest X-ray (February 1978) showing extensive pleural thickening on the right

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THE BRITISH THORACIC ASSOCIATION

A meeting of the Association was held at the Royal College of Physicians on Friday 8 December 1978. The following papers were presented.

Demeclocycline in Treatment of the Syndrome of Inappropriate Secretion of Antidiuretic Hormone

W. H. Perks, H. Walters and K. Prowse

City General Hospital, Stoke on Trent

The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has become increasingly recognized as a cause of confusion and stupor in patients with a wide variety of diseases. Treatment of SIADH improves the quality of life and makes for easier nursing even in terminal malignant disease. Until recently the only effective means of therapy has been fluid restriction or treatment of the primary condition. We report here our experiences over two years in the treatment with demeclocycline of 14 patients fulfilling the criteria for the diagnosis of SIADH.

Demeclocycline 1200 mg returned the serum sodium to normal (> 135 mmol/litre) in all patients after a mean of 8.6 days (SD ± 5.3 days). There was a moderate rise in blood urea from 4.2 mmol/litre (SD ± 2.3) before treatment to 10.1 mmol/litre (SD ± 5.1) ($P < 0.001$) after 10 days to a maximum of 13.4 mmol/litre (SD ± 6.8). In four patients the urea rose above 20 mmol/litre (normal range 2.5–5.8 mmol/litre) and therapy with demeclocycline was discontinued because of this in two patients. The azotaemia could be attributed to a combination of increased urea production and a mild specific drug-induced nephrotoxicity. Discontinuation of demeclocycline in six patients lead to a fall in serum sodium, in one case precipitously, and return of the urea towards normal levels.

Demeclocycline appears to be an effective treatment of SIADH and the risk of azotaemia although real, is a small price to pay for ease of patient management, particularly in a terminal illness.

Theophylline in Asthma: What Dose? What Plasma Level? What Use?

P. W. Trembath and S. W. Boobis

St Bartholomew's Hospital, London

There has been little systematic study of theophylline pharmacokinetics, and the relation between plasma drug levels and pharmacological effect, until the last few years. A good correlation between plasma theophylline level and bronchodilatation in asthma has now been established, although the effect achieved at any particular plasma level varies considerably between patients. Consequently, the determination of plasma theophylline levels offers a useful, but not absolute, guide to the expected therapeutic effect. The usually recommended therapeutic range of plasma theophylline levels is 10–20 μg/ml, although a useful and adequate bronchodilator response may often be achieved with plasma levels of 5–10 μg/ml.

We have found considerable between-subject variation of theophylline kinetics in a group of 12 healthy volunteers given intravenous aminophylline: the plasma (theophylline half-life varied from 3.4 to 8.4 hours (mean 5.8 hours). Administration of an oral sustained-release aminophylline formulation (Phyllocontin) also resulted in marked differences in peak and trough plasma theophylline concentrations during 'steady state' conditions although some of this variation would have been due to differences in body weight. Five doses of 225 mg 12-hourly resulted in peak levels of 5.9–15.5 μg/ml (mean 9.7 μg/ml) and trough levels of 2.7–8.0 μg/ml (mean 4.9 μg/ml) during the fifth 12-hour dose interval. In five subjects, the respective peak and trough levels after five doses of 450 mg 12-hourly were 17.5–23.6 μg/ml and 4.3–15.4 μg/ml. Optimal plasma theophylline levels were achieved between daily doses of 7.5 and 15 mg/kg body weight.

The estimation of plasma theophylline levels may be of particular use in critically sick patients receiving aminophylline infusion, in out-patients, to assist in evaluating side effects, compliance, and whether an increase in dose will be safe, and finally in clinical trials of theophylline preparations.

Comparative Pharmacokinetics of Two Theophylline Derivatives in Asthmatic Patients

Roy W. Jones
Cardiothoracic Institute, London

Nineteen patients with chronic asthma were studied. Plasma theophylline level was compared with PEFR and FEV_1 for 10 hours following either 600 mg of choline theophyllinate (Choledyl, $n=10$) or 450 mg of slow-release aminophylline (phyllocontin, $n=9$). Six patients taking choline and six taking aminophylline were restudied following one month's treatment with the drug.

Patients receiving choline showed marked peak plasma levels followed by fairly rapid decline to subtherapeutic levels, whereas slow-release aminophylline gave sustained therapeutic levels without marked peaking. No significant change in the handling of either drug was seen following the one month's treatment.

Significant correlation was seen between the mean theophylline level following slow-release aminophylline and the mean percentage improvement in PEFR and FEV_1 but this could not be shown for choline theophyllinate.

Following the single dose studies, side effects were only seen in patients receiving choline theophyllinate and were associated with the peak plasma theophylline level. In view of the long plasma half-life (mean value 9.16 hours) with slow-release aminophylline, side effects due to accumulation may occur during long-term treatment and this was seen in three patients. However, since there is no marked peaking effect it should be possible to eliminate these side effects by small reductions in dosage with minimal loss in therapeutic benefit.

Slow-release aminophylline seems to offer several advantages over short-acting preparations, though further clinical trials are necessary to confirm its therapeutic effect.

Studies of Regional Lung Function During Fibreoptic Bronchoscopy

D. M. Denison, S. J. Williams,
N. J. H. Davies and R. J. Pierce
Brompton Hospital, London

We have developed a number of techniques to measure the size, shape, position, ventilation and perfusion of individual lungs, lobes and segments which have proved particularly useful in assessing patients before chest surgery. These techniques make use of the combination of a fibreoptic bronchoscope and a mass spectrometer, gamma camera and flow volume loop recorder. The probe of a mass spectrometer can be passed through the suction channel of the fibreoptic bronchoscope and into a lobar or segmental bronchus. It can then be used to sample respiratory gases or show the fate of gases injected into parts of the lung or inspired at the mouth. Lobar or segmental bronchi can be obstructed by inflating the balloon of an occlusion catheter and the occluded or unoccluded parts of the lung studied independently. Krypton 81m can be diverted down the suction channel of the bronchoscope and because of its short half-life can be used to visualize different parts of the lung in rapid succession. Examples of patients who have been studied with these techniques were shown.

Legionnaires' Disease: Microbiology

A. D. Macrae
University Hospital, Nottingham

The causative bacterium of legionnaires' disease pneumonia—*Legionnella pneumophila*—is a small Gram-negative organism, slow-growing and with fastidious cultural requirements. It appears to be a distinct species with at least four serogroups. Its isolation from patients presents difficulties. It has been recovered from the pleural exudate of immunosuppressed patients but in other patients such exudates are uncommon. Most isolates have come from lung tissue of fatal cases and to a less extent from open lung biopsies. Culture has been by a combination of methods including guinea-pig intraperitoneal inoculation, injecton into the yolk sacs of fertile hens' eggs and the use of selective bacteriological media. The organisms have, with some difficulty, been demonstrated in small numbers of sputum samples and trans-tracheal aspirates but such procedures cannot yet be said to be widely available.

In consolidated areas of lung, as either unfixed or formol-fixed tissue, the organism can be detected by specific fluorescent antibody test, by negative stain electron microscopy and less specifically by Giemsa or the silver impregnation (Dieterle) staining method. As most patients recover, a diagnosis can be confirmed retrospectively by serological tests. At present an indirect fluorescent antibody method, first described from CDC, Atlanta, is used. With suitably taken blood samples patients should show a four-fold or greater rise in antibody titre during the course of illness. Less ideally, a presumptive diagnosis may be made from a single high titre sample taken during convalescence.

The natural habitat of the organism and its prevalence are still obscure. Efforts are being made to investigate whether human exposure and infection occur without development of pneumonia.

Legionnaires' Disease: Clinical Features

A. C. Miller
City Hospital, Nottingham

As with other bacterial pneumonias, factors predisposing to legionnaires' disease are (*a*) increasing age (mean 50·5), smoking, heavy alcohol consumption, and (*b*) underlying malignancy (especially lymphoma and leukaemia), corticosteroids and other immunosuppressants, and severe cardiorespiratory disease. Not surprisingly, death is common in the latter group. Infection is commoner between June and November (80%), and in males (70%). After an incubation period of 2–10 days, onset is usually acute, with 3–7 days' pyrexia, sweating and anorexia. Common symptoms are cough (often non-productive), dyspnoea, chest pain (often pleuritic), diarrhoea, myalgia, headache and confusion.

Hospitalized patients are pyrexial ($>39°C$), with radiological consolidation usually apparent clinically also. Findings much commoner than in lobar pneumonia due to other pathogens are diarrhoea (30%), confusion (40%), lymphopenia ($<1000/mm^3$) (65%), hyponatraemia (<130 mM/litre) (65%), hypoalbumenaemia (<25 g/litre) (70%), abnormal liver function tests (70%), microscopic haematuria (50%), and radiological extension in spite of therapy (50%). When several of these are present, a working diagnosis can be made during the acute stage in most cases.

Management is similar to that for other pneumonias and many patients improve rapidly whichever antibiotic is used. However, in others radiological extension is accompanied by respiratory failure requiring assisted ventilation, renal failure requiring dialysis or increasing drowsiness and confusion. In some series mortality, 15–20% of hospitalized cases, is lower with erythromycin than other antibiotics. In immunocompromised patients it should be given for at least two weeks, initially intravenously, and rifampicin should be added if response is unsatisfactory; in this group superinfection with other pathogens is common and lung abscesses may develop. Full doses of immunosuppressants can be continued in renal transplant recipients.

Survivors usually return to their former health, although persisting lung damage is common as shown radiologically, by reduction in diffusing capacity and by pathological studies. Most have amnesia for the early days of hospitalization.

Legionnaires' Disease: Radiology

W. H. Roderick Smith
City Hospital, Nottingham

The chest radiographs of 21 cases of proven legionnaires' disease seen in Nottingham have been reviewed. Ill-defined segmental consolidation was the earliest change in four patients, whilst the remainder presented with more extensive lesions. In 15 patients the disease was initially unilateral, but it spread to involve the opposite lung in six cases. In the remaining cases both lungs were affected when the patient was first seen. During the illness more than one lobe was involved in two-thirds of the cases and extension to previously unaffected parts of the lungs was common. The consolidation was often extremely dense and air bronchograms were seen in several cases. Pleural effusion was only seen once, which is unlike the findings in some American outbreaks. Cavitation did not occur.

Slow resolution was a feature of the disease. Only one radiograph was clear within a month of the onset of the illness and by four months only half the radiographs had cleared. This slow resolution resulted in five of the patients being referred for bronchoscopy to exclude an underlying tumour.

Legionnaires' Disease: Epidemiology

C. L. R. Bartlett
Communicable Disease Surveillance
Centre, Colindale, London

Legionnaires' disease had occurred both sporadically and in large common-source outbreaks. The disease is widely distributed, cases having been reported from North and South America, Europe, Israel and Australia. In Great Britain legionnaires' disease has presented predominantly as sporadic illness, the only outbreak to be identified occurred in 1973, among tourists returning from a package holiday in Benidorm, Spain.

Twelve outbreaks have been reported in the USA with an overall attack rate in the region of 2%. There is now overwhelming evidence for airborne spread. It is likely that air-conditioning systems may have served as vehicles for dissemination of antigen in some instances. On four occasions an organism closely resembling the legionnaires' disease bacterium has been isolated from the evaporative condensor or cooling tower of the air-conditioning plant at the site of an outbreak.

More than a hundred sporadic cases have now been identified in Great Britain. The age/sex distribution shows a preponderance of middle-aged males. A high proportion were heavy smokers and many had underlying respiratory disease. Seasonal variation has occurred with peak incidence in the late summer months. A similar pattern has been observed in the USA, among both sporadic and outbreak cases. Person-to-person spread appears to be exceptionally rare and has not been observed in Great Britain.

Actions of the Respiratory Muscles

G. J. Gibson
Freeman Hospital, Newcastle upon Tyne

The diaphragm which is the major inspiratory muscle also has an important role as the inferior surface of the chest wall. It may be moved passively or may be displaced by active contraction when its 'wall action' enlarges the thoracic cavity; in addition it has an 'insertional action' on the lower ribs. The actions of the diaphragm on the rib cage have been a matter of controversy and are potentially both inspiratory (by direct insertion and by increasing abdominal pressure) and expiratory (by lowering pleural pressure). The nett effect in erect normal subjects is inspiratory and proportional to the increase in abdominal pressure produced by diaphragm descent. During normal breathing the intercostals probably exert a stabilizing influence on the ribs and, in the absence of intercostal activity, paradox of the upper rib cage may occur.

When the diaphragm is paralysed the intercostal and accessory muscles expand the lungs and rib cage at the expense of upward displacement of the diaphragm; the abdominal pressure consequently becomes more negative during inspiration and the anterior abdominal wall shows inward paradoxical movement. The consequences of paralysis of the diaphragm are move evident in the supine posture.

Although the abdominal muscles are expiratory they may aid the inspiratory muscles by modulating diaphragm length when ventilation increases in normal subjects; in patients with diaphragm paralysis relaxation of abdominal muscles at the start of inspiration may produce passive descent of the diaphragm.

The Physiology of Scoliosis

G. J. R. McHardy
City Hospital Edinburgh

Severe scoliosis interests respiratory physicians, because of the respiratory disability, pulmonary hypertension and respiratory failure to which it gives rise. Recent work, particularly that of Kafer (1975, 1976, 1977) has helped us to understand some of the ways by which mechanical and developmental defects eventually affect pulmonary gas exchange and respiratory control.

Idiopathic scoliosis comes on in childhood often before development of the lungs or skeleton is complete. As a result abnormalities of alveolar volume and distribution of pulmonary vessels may occur in compressed parts of the lungs. Vital capacity and total lung capacity are reduced, in proportion to the angle of spinal curvature. Difficulties arise in predicting normal values for comparison because of the effect of the spinal curve on height, but allowance can be made for this. The severity of the spinal curve is also reflected in impaired body growth and, in turn, height and weight, and angel of curve are correlated with the compliance of the respiratory system and its components.

In careful studies of a large number of scoliotics over a wide age range, Kafer was able to demonstrate abnormalities in respiratory control and gas exchange. The slope of the hyperoxic rebreathing CO_2 response curve (S_{CO_2}) was lower than in normal subjects and there was a suggestion that S_{CO_2} declined further in older patients. Arterial P_{O_2} was inversely correlated with angle of curve and with age, and fell by up to 0.6 kPa per decade, a greater decline than in normal subjects. Similarly, arterial P_{CO_2} was found to rise with age by about 0.4 kPa per decade. The alveolar–arterial P_{CO_2} difference, an index of poorly ventilated lung areas, increased with falling vital capacity, but not with age, suggesting that, in addition to any reduction in arterial P_{CO_2} due to the effects of impaired distribution, the fall in P_{CO_2} with time could be largely attributed to the gradually rising P_{CO_2}. With increasing age, the proportion of wasted ventilation, the dead space/tidal volume ratio, also increased.

The defects in mechanical and gas exchanging function of the lungs combine and, with pulmonary hypertension, contribute to the end-stage of 'heart failure of the hunchback'. Despite this clearer picture many others still require further investigation, particularly skeletal and respiratory muscle function, the course of changes in function in individuals over a number of years, the effects of corrective operations (which though cosmetically valuable may do little to improve function itself) and the differing times of onset of cardiac and respiratory failure in patients with seemingly comparable disability.

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Pulmonary Hypertension and Scoliosis

J. M. SHNEERSON
Westminster Hospital, London

Pulmonary hypertension is a frequent long-term complication of scoliosis. Right ventricular hypertrophy is present in 65% of moderate or severe scoliotics at autopsy (Shneerson et al. 1978). Bergofsky et al. (1959) first showed that pulmonary hypertension was analogous to the cor pulmonale of chronic pulmonary disease, in that the pulmonary vascular resistance was raised. The cause of this is still uncertain.

The pulmonary artery pressure has been measured in 40 scoliotics, none of whom had any cardiac or respiratory disease complicating the scoliosis. A Bradley microcatheter was passed into the pulmonary artery and the pressure measured at rest and during a progressive exercise test on a bicycle ergometer. Eleven of the patients repeated the procedure while breathing pure oxygen.

The pulmonary artery pressure at rest was raised in only 28% and was inversely related to P_{aO_2}. Inspiration of pure oxygen lowered the pressure by up to 16 mmHg. In contrast the rate of rise of pressure during exercise was abnormally rapid in 76%. It was inversely related to VC, FRC and TLC, but was only slightly improved by inhaling pure oxygen during exercise. The pulmonary vascular bed appears to accommodate the resting cardiac output with a normal pulmonary artery pressure unless hypoxaemia is present. However, when the lung volume is severely diminished, the pulmonary vasculature is anatomically too small to prevent a rise in pulmonary artery pressure as the cardiac output increases during exercise.

BERGOFSKY, E. H., TURINO, G. M. & FISHMAN, A. P. (1959) *Medicine, Baltimore*, *38*, 263.
SHNEERSON, J. M., SUTTON, G. C. & ZORAB, P. A. (1978) *Clin. Orthop. related Res.* In the press.

Surgical Treatment of Chest Deformities

R. J. M. MCCORMACK
City Hospital, Edinburgh

Deformities of the sternocostal part of the chest wall are not rare. The most common deformity is pectus excavatum or funnel chest; pectus carinatum or keel chest is the next most common. Together they account for over 90% of these deformities. Rare lesions include absence of ribs and/or of the sternal head of pectoralis major.

Even when severe, these lesions rarely produce cardiac or respiratory symptoms. Ventilation studies demonstrate some reduction in vital capacity and forced expiratory volume, as one would expect. The most important aspect of the deformity is the marked psychological problems that it commonly causes and for this reason alone surgical correction is usually advisable.

The operation involves the removal or mobilization of the deformed cartilages, osteotomy of the sternum to allow its replacement and some form of support to retain the sternum in the corrected position. Even with predominantly unilateral deformity, the operation nearly always needs to be bilateral. Results are good, although a completely normal chest shape is rarely achieved. Morbidity is small and mortality nil. Patients are usually well satisfied and sometimes elated by the postoperative appearance.

The deformities and results are illustrated by the experience of the Edinburgh Thoracic Unit, where 60 such deformities have been dealt with surgically in the last 20 years.

Forensic Aspects of Lung Disease

B. Knight
University Hospital, Cardiff

The medicolegal aspects of thoracic lesions fall into two main groups: (*a*) trauma to the thoracic cage and its contents and (*b*) disease of both the cardiovascular and the pulmonary systems. The major medicolegal interest in lung disease is naturally related to industrial exposure, especially the pneumoconioses, which have particular significance in compensation and civil litigation.

Trauma to the chest is extremely common in accidents, suicide and homicide. The most florid forms of asphyxia occur in compression of the chest; penetrating injuries, especially by a knife, constitute the largest single mode of homicide in Britain. Pneumothorax and intrapulmonary and intrapleural haemorrhage constitute the main risks.

Injuries to great vessels are also extremely common. Another pulmonary condition subject to considerable forensic controversy is the finding at post-mortem of gastric contents in the air passages, the significance of which is in dispute in many cases.

The problem of industrial exposure to various noxious agents has considerable medicolegal significance and that from mining, quarrying and other dust-producing occupations is high on the list of medicolegal problems. There is a tendency to over-value the pathological findings and these must be strictly classified and taken in conjunction with the clinical picture. The relationship of tumours, especially carcinoma and mesothelioma, to asbestos exposure is a matter of current interest, but the pathology is not always clear-cut and the medicolegal significance sometimes confused.

Other toxic agents which sometimes give rise to medicolegal complications include cadmium, beryllium and substances such as paraquat, the latter having been involved in at least one homicide.

In summary, though the forensic aspects of chest diseases and trauma are difficult to classify, they constitute a numerically common problem in coroner's pathology and necessitate a wide understanding of the pathological processes involved.

Diagnostic Accuracy of Cytology and Biopsy in Primary Bronchial Carcinoma

C. R. Payne, P. G. I. Stovin and J. E. Stark
Papworth Hospital, Cambridge

The accuracy of diagnosis of cell type by cytology and biopsy techniques in 161 cases of confirmed primary lung cancer, seen at Papworth in the years 1974–7 inclusive, has been examined. Tissue for final diagnosis was obtained by thoracotomy in 138 and by autopsy examination in 23 cases. Methods used in investigation were cytological examination of sputum bronchial aspirate and percutaneous needle aspiration biopsy, and histological examination of tissue obtained by bronchial biopsy. All patients had one or more investigations and all bronchoscopies were performed with the rigid bronchoscope.

The true histological type was taken to be that of the surgically resected or autopsy specimen, and the cell type diagnosis obtained by investigation (the presumptive diagnosis) was compared with this true histological type. Tumours were classified as squamous cell carcinoma, oat cell carcinoma, adenocarcinoma, adenosquamous carcinoma or undifferentiated carcinoma.

The presumptive diagnosis was correct in 37 (88%) of 42 cases investigated by sputum cytology, in 42 (84%) of 50 cases investigated by bronchial aspirate, in 49 (80%) of 61 cases investigated by bronchial biopsy and in 11 (48%) of 23 cases investigated by percutaneous needle aspiration biopsy. Percutaneous biopsy was the most effective means of obtaining carcinoma cells by investigation but the least accurate because of particular difficulty experienced in the diagnosis of adenocarcinoma by this method.

We have also examined the diagnostic accuracy achieved in each histological type. Greatest accuracy (80–90%) was achieved in patients with squamous carcinoma, the commonest diagnostic error in this group being undifferentiated carcinoma. The accuracy of diagnosis of adenocarcinoma was poor, only nine (20%) of 45 cases being correctly diagnosed by investigation. The commonest incorrect diagnosis was squamous cell carcinoma. All 11 presumptive diagnoses of undifferentiated carcinoma were incorrect, each of these tumours being given a more specific cell type diagnosis on examination of the resected or autopsy specimen.

A Comparison of Ampicillin and Amoxycillin in Acute on Chronic Bronchitis

G. Anderson, A. G. Jariwalla,
J. Saour and J. Glencross

Newport Chest Clinic

Thirty-one patients with acute exacerbation of chronic bronchitis were entered in a double-blind study of amoxycillin 1.5 g compared with ampicillin 4 g daily. Twenty-five patients completed the study and after treatment for one week there were no significant differences between the treatments in the rates of achieving mucoid sputum, reduction in sputum volume, improvement in peak expiratory flow rate or duration of hospital stay. The incidence of side effects was minimal with both drugs.

In the doses studied, ampicillin and amoxycillin are effective drugs of approximately equal cost. The current BTA comparison between these two drugs utilizes quite different dosage schedules and may produce different results.

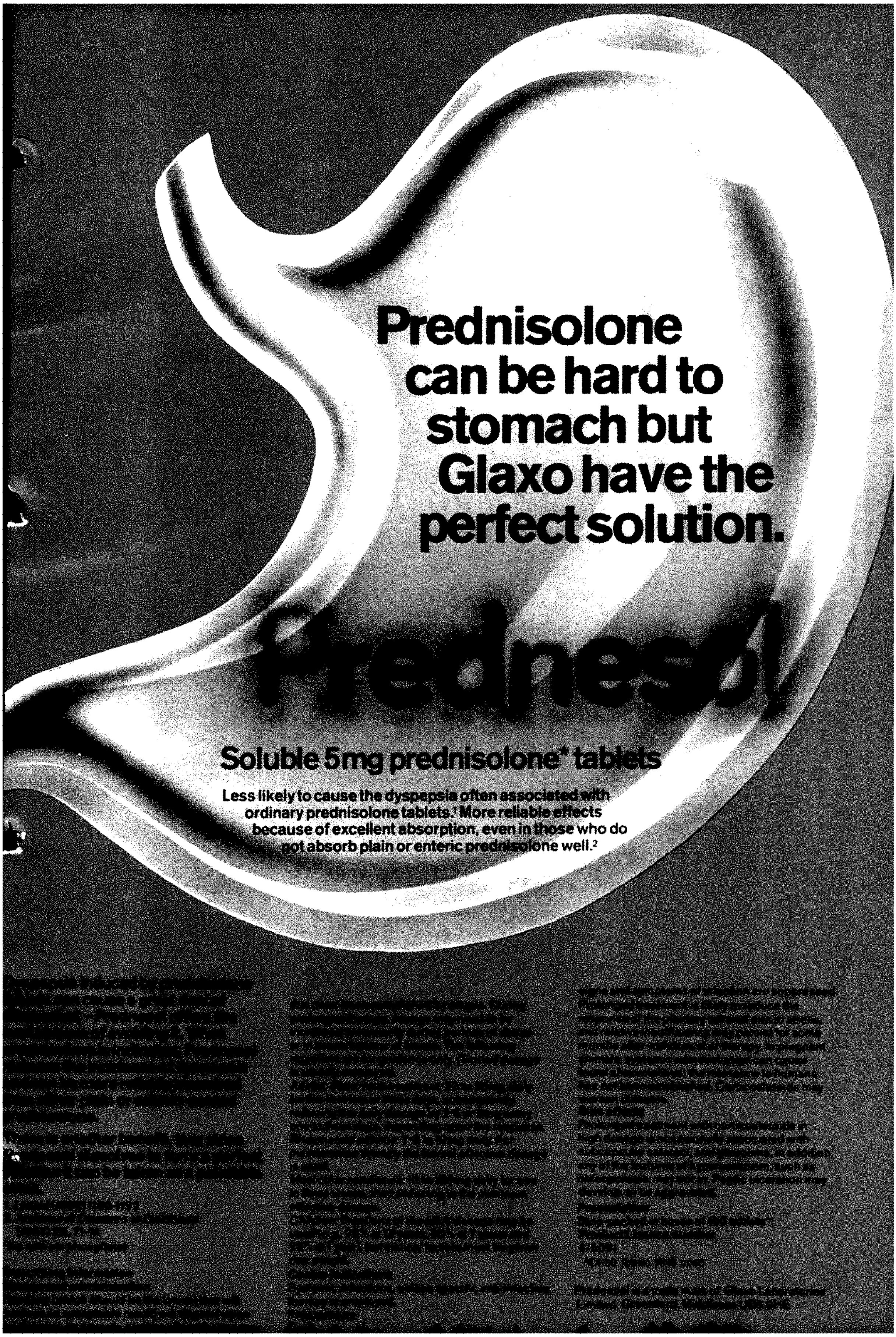
FUTURE MEETINGS OF THE BTA

1–5 July 1979	Annual Conference, Churchill College, Cambridge. Jointly with the Swedish Thoracic Society.
7 December 1979	London Meeting, Royal College of Physicians
9–11 April 1980	Annual Conference, University of Swansea
10–13 September 1980	Autumn Meeting, Lillihamer, Nr Oslo, Norway. Jointly with the Norwegian Thoracic Society
5 December 1980	London Meeting, Royal College of Physicians (to be confirmed)
29 June–2 July 1980	Annual Conference, Churchill College, Cambridge. Jointly with the Chest, Heart and Stroke Association and the European Region of the International Union against Tuberculosis
30 June–3 July 1982	Annual Conference, University of York. Jointly with the Thoracic Society.

Long-term Care of the Patient with Chronic Respiratory Insufficiency

A working party of the Thoracic Medicine Committee of the Royal College of Physicians with support from the British Thoracic Association and Thoracic Society has been set up to review this subject including: (*a*) prevalence of and social burden from chronic respiratory insufficiency; (*b*) prophylaxis and protection against aggravating factors; (*c*) intervention procedures (e.g. drugs, oxygen, physiotherapy, etc.); (*d*) aids to increased activity; and (*e*) social support and aids to employment. The subsequent report will be directed to improving the quality of long-term care including the needs for more research.

Please will you help the working group by submitting evidence or views on any relevant topic. The comment should be brief (not more than one side of A4 paper) and sent to Dr J. E. Cotes, Pneumoconiosis Research Unit, Llandough Hospital, Penarth, Glam. Your help will be much appreciated and warmly acknowledged.



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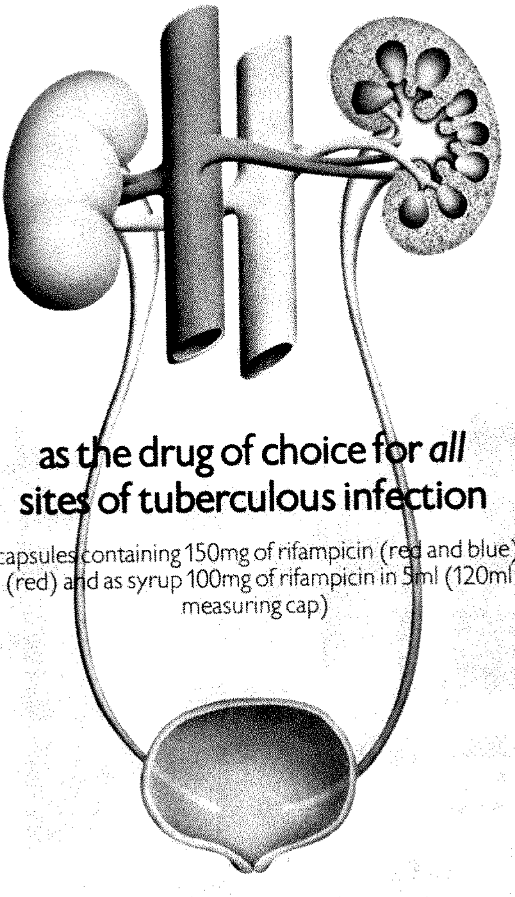

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BOOK REVIEWS

Correction

We wish to correct an attribution in a recent book review of *Lung Biology in Health and Disease, 3. Bioengineering Aspects of the Lung*. The final paragraph of this review implies that the National Institutes of Health (NIH), an agency of the United States Government, was involved in the preparation and issuance of the series of which this volume is a part. Dr Claude Lenfant, the editor of the series, although the Director of the Division of Lung Diseases at the NIH, undertook this editorship as an independent activity. It bears no relationship to his responsibilities as an administrator in a federal agency.

Pulmonary Tuberculosis: A Journey Down the Centuries

R. Y. Keers

London: Baillière Tindall. 1978. Pp. x+265. Price £11.50

There must be many chest physicians with retirement looming on the horizon who have day-dreams of spending their enforced leisure hours writing the definitive history of tuberculosis. Only their generation is now able to write it; only their generation has experienced and can adequately appreciate the extent and the drama of the tremendous changes that have taken place, in a single medical lifetime, in the management of this disease and in the problems it raised. Their day-dreams, however, have now been shattered; Dr Keers has got in first with *Pulmonary Tuberculosis: A Journey down the Centuries*.

There can be few who are now more qualified to write this story than Dr Keers. His experience extends from the grim 1930s when the sanatorium, enforced rest in bed, collapse therapy and the tuberculosis dispensary formed the main defence against the disease, which was still then the most common cause of death and disability.

It was in those days a disease which was difficult to prevent and hardly ever considered curable. It was rife amongst the underfed and overcrowded, but it ravaged all classes and at all ages. Rapidly improving social conditions, more effective contact examination, the introduction of BCG vaccination and finally chemotherapy all reduced the 'white plague' to what is now in the Western world an uncommon disease. In developing countries it is still a serious problem and may remain so certainly for the rest of this century.

Dr Keers writes very clearly and graphically. He describes the effects of this disease on mankind from the earliest days down to modern times; he has taken over where most other historical accounts of tuberculosis have stopped, and has brought us up to date. His final chapter, The Last Frontier, is a lucid account of the problems which now face developing countries.

Dr Keers is to be congratulated on having written a fascinating story which is a pleasure to read. It should appeal to both medical and non-medical readers. Many physicians, nurses and others, concerned with the management of this disease in the past and now, will want a personal copy of this book. It is attractively produced; it is also expensive, but worth every penny.

M. CAPLIN

Modern Problems in Paediatrics, 19. Mucus Secretions and Cystic Fibrosis

G. G. Forstner

Basel: S. Karger, 1977. Pp. viii+217. Price SFr 111

This, the nineteenth volume of a series devoted to modern problems in paediatrics, is the report of the first Canadian Cystic Fibrosis Conference held at Kimberly, Ontario, in October, 1976, and devoted to mucus secretion.

The first half is concerned with normal mucus glycoproteins, their composition, physical properties, synthesis and secretion. The second half describes mucus secretion and clearance in cystic fibrosis.

Research into the quantity and quality, the control of secretion and the flow characteristics (the dynamics and rheology) of mucus is highly complex in the normal let alone the abnormal. In this volume excellent contributions make it abundantly clear to those not in the field that we are yet only on the threshold of understanding structure and function of mucus. How can we expect any rationale, therefore, to the use of pharmacological agents in the modification of mucus secretion? Prospects in the field of mucus secretion are exciting and this is an extremely valuable, stimulating and well documented book of reference in this difficult field.

J. C. BATTEN

Congenital Deformities of the Chest Wall and Their Operative Correction

Mark M. Ravitch

Philadelphia: Saunders. 1977. Pp. viii+306. Price $22.50

It is unusual to find a complete historical account of the description of a disorder and its management and an extensive review, not only of the literature on the subject, but also of the modern approach to its treatment, all within one cover.

Mark Ravitch has put many years work into this book and his approach to the subject is novel and interesting. Chapters on pectus excavatum and carinatum and sternal clefts form the major part, with short chapters on rarer entities, Poland's syndrome and thoracic defects in generalized skeletal deformity.

Each chapter begins with an historical account of the subject: experimental work is not extensive in this field, but postulated causes and any supporting evidence are presented. This is followed by illustrative case histories and modern approaches to investigation and aspects and views on surgical correction. The amount of work which has been put into the book is demonstrated by the sixteen closely typed pages of references (which we are told are only the most important) and long tracts of collected case reports. Original descriptions from antiquity are always interesting and are reproduced (with inevitable photograph of the original writing) and their accompanying illustrations. Case histories, with clinical photographs, radiographs and follow-up for up to thirty years after surgery, are included. Operative techniques are well illustrated and easily followed.

One cannot but feel, however, that much of the information is superfluous. Are seventy photographs and twenty-four radiographs of pectus excavatum really all contributory? There are ten pages of authors' descriptions of symptoms associated with the deformity and forty pages of different operations for correction, most of which, we are told, are only of historical interest. Deformities of the chest wall are uncommon and few surgeons are likely tó accumulate much personal experience. A wealth of clinical material has been related here, but it would greatly benefit from précis and summary.

Symptomatic indications and benefits of correction are stressed throughout the book, but where physiological mechanisms are mentioned in support it is without scientific evidence. There must be sufficient information to warrant conclusions, for instance on the optimum age, indications for surgery and the physiological effects, but unfortunately this information is not made clear.

It is a pity that after so much work by the author this book is not more clinically informative. It is largely anecdotal and must remain mainly of historical interest.

ROGER FRANKS

Mechanical Concepts in Cardiovascular and Pulmonary Physiology

Jerry Franklin Green

Philadelphia: Lea & Febiger (London: Henry Kimpton). 1977. Pp. xiv+166. Price £7.00

This book was written for 'those serious students who wished to obtain a firm conceptual understanding of the physiology of the systemic circulation and the lung'. The author's main aim is to instil a clear understanding of the relationships between flow, vascular pressures and volumes in a branching system of blood vessel. After explaining fairly simply the basic equations, he goes on to state the simple volume/pressure relationships and then to explore the behaviour of elementary 'models' of the circulation. The mechanical properties of the different parts of the circulation are then considered; next, the behaviour of the heart as a pump is treated briefly and the whole circulation is described at the end. Experimental data are quoted throughout to justify the assumptions.

The approach is developed from the teaching of Permutt, Riley, Bronberger-Barena and others at Johns Hopkins in the late 1960s. I enjoyed this teaching at the time and it has certainly helped me to understand the arguments for and against the use of different agents in the treatment of circulatory and cardiac failure. The concepts outlined in the book form the basis for understanding the control mechanisms with which so many accounts of this subject begin.

The section on the lung is less successful, perhaps because it is contained in thirty-five rather than eighty pages. Dr Green repeats the traditional account of thoracic compliance. Airway collapse is discussed according to the analysis of Pride and Permutt. Mead's equal pressure point is mentioned in a figure but without any reference. It is useful to show how airway resistance may be derived from maximum expiratory flow, but methods actually used to measure airway resistance are not mentioned. The section on basic mechanics does not include a discussion of laminar and turbulent flow, so the beginner would find little basis for understanding the arguments about the interpretation of flow–volume loops and the effects of breathing low-density gas mixtures on pulmonary function.

There is some merit in pointing out the similarities in blood and air flow, but a somewhat different approach is needed for the study of the lungs than for the circulation. Dr Green would do well to discuss with his colleagues in clinical physiology how this section could be made more useful to the majority of those interested in the function of the human lung.

This book can be recommended to those embarking on a career as professional physiologists, whether 'pure' or clinical, and to teachers planning courses in clinical cardiovascular physiology. G. LASZLO

Muscular Exercise and the Lung

Jerome A. Dempsey and Charles E. Reed

Madison, Wis.: University of Wisconsin. 1977. Pp. viii+406. Price £15.00

This book details the proceedings of a three-day conference on muscular exercise and the lung. It consists of five separate sections: the respiratory muscles and breathing mechanics; mechanisms of exercise hyperpnoea; control of airway calibre; exercise-induced bronchospasm; and pulmonary gas exchange. Each section contains four to six contributions by scientists well established in their respective fields. The individual texts are well referenced and include whatever discussion followed, together with a more complete discussion section at the end of each major section, and a final concluding chapter summarizing the entire meeting.

There is no doubting the quality of many of the individual contributions. In the first section Goldman summarizes well the advantages of measuring electrical and mechanical events in muscle simultaneously and Grimby's chapter on the place of muscle as a limiting factor to exercise is excellent. The chapter on Modelling the Respiratory System (Grodins) is most complex and requires a far greater grasp of mathematical concepts than the average 'Physiologist, Clinician, Chest Physician, Allergist and sports medic' that the book should it claims 'be of immediate and lasting interest to'.

The most stimulating section of the book is the second section on the mechanisms of exercise hyperpnoea where the advocates of neural drive, whether from central or peripheral stimuli or both (Kao, Eldridge) and those of CO_2 and ventilatory drive present concise reviews with interesting experimental data from their laboratories (Wasserman).

In the section on control of airway calibre Sampson et al. discuss the effects of the rapidly adapting vagal receptors in intrapulmonary airways, and present interesting new data.

The fourth section on exercise-induced bronchospasm was the most straightforward part of the book as the phenomenon is now common knowledge and the contributors all reviewed their established work (McFadden, Godfrey, Bierman) with very little new and no convincing attempt to explain the basic phenomenon.

The final section on pulmonary gas exchange is well presented with a review of the roles of ventilation/perfusion and diffusion both in health (Gledhill) and disease (Wagner).

Each of the five sections in this volume covers an extensive amount of ground. However, each contribution is short and the data, often personal, tend to be presented with too little discussion of the important controversies.

The small crowded type does not make the book any easier to read, crammed with facts as it is. I found it slow going but a worthwhile experience, although I suspect that its major appeal will be to the physiologist interested in respiratory muscles, ventilatory drive and exercise rather than the wider, more clinically orientated reader it hopes to reach.

STEPHEN G. SPIRO

Dynamic Bronchoscopy

M. A. de Kock

Berlin: Springer. 1977. Pp. x+118. Price DM 112

The author describes his experience with bronchoscopy in South Africa. After a brief description of bronchial anatomy, the equipment used and the technique of bronchoscopy are described in great detail. He regards rigid bronchoscopy as the most useful technique, fibreoptic bronchoscopy being complementary to it. The anaesthetic methods are discussed, and he comes down in favour of the use of 'local', although he admits that general anaesthesia is more pleasant and perhaps its risks are over-stressed. The normal movements of the bronchial tree in a patient who is breathing spontaneously are described. There are then several brief chapters on the findings in such diseases as tumours or tuberculosis. This is all done in the first 41 pages. The remainder of the book is taken up with a series of figures and complementary photographs which are of a very high standard and must be derived from an enormous collection. The method of presentation is very similar to that of other books on the subject, and, apart from the excellence of the photography, it does not seem to me that the book has a great deal new to say.

J. R. BELCHER

The Human Pulmonary Circulation

Peter Harris and Donald Heath

Edinburgh: Churchill Livingstone. 1977. Second edition. Pp. xiv+712. Price £28.00

The observation that the second edition of this excellent work is different from the first is easy to make on a variety of grounds. It weighs 1 kg more, it has larger pages (with improved typography) and contains an additional twelve chapters. The number of pages has been increased from 340 to over 700 and the binding is of better quality. Like its predecessor, the printing is on art paper and the standard of the plates is high, particularly the reproduction of transmission electron micrographs. It is also much more expensive, reflecting developments unrelated to the pulmonary circulation.

This edition preserves the original concept of relating microscopic and macroscopic form to organ function, calling in all the related physical sciences.

The additional chapters reflect the experiences of the authors during the past decade: from their studies in the Andes come contributions on the pulmonary circulation at high altitude, the structural changes of hypoxic pulmonary hypertension and a chapter on the role of chemoreceptors in the pulmonary circulation. The work carried out by Heath and his colleagues on pulmonary hypertension produced by ingested materials (e.g. *Crotalaria spectabitis*) is clearly reviewed in Chapter 27.

The increasing use made of transmission electron microscopy during the last ten years is reflected in the book, which now has several good electron micrographs appropriately described.

The use of radioactive gases is now described in a chapter on the regional distribution of blood flow. A minor infelicity, commonly seen, occurs in this chapter in which the authors inject a solution of xenon in saline into a vein, and then describe it as being so insoluble in blood that it passes almost entirely into the gas phase. The common confusion between solubility and partition coefficient is neatly exemplified.

The short account of the structure and function of vascular smooth muscle reflects the increasing interest of one of the authors in biochemical mechanisms.

Concepts about the interstitial space in the lungs have undergone some change and the chapter on this topic, coupled with that of pulmonary oedema, covers the subject well. In view of the disparity of view about what precisely constitutes the interstitial space it is surprising to find no specific definition of the term. It can, however, be found by inference. The double indicator dilution technique for the measurement of extravascular lung water is described, together with the observation that the technique underestimates this value. The more recent work from the Pisa group which shows a good correlation probably appeared too late for inclusion in the book.

The authors have preserved the readability of the book and the second edition is undoubtedly better than the first.

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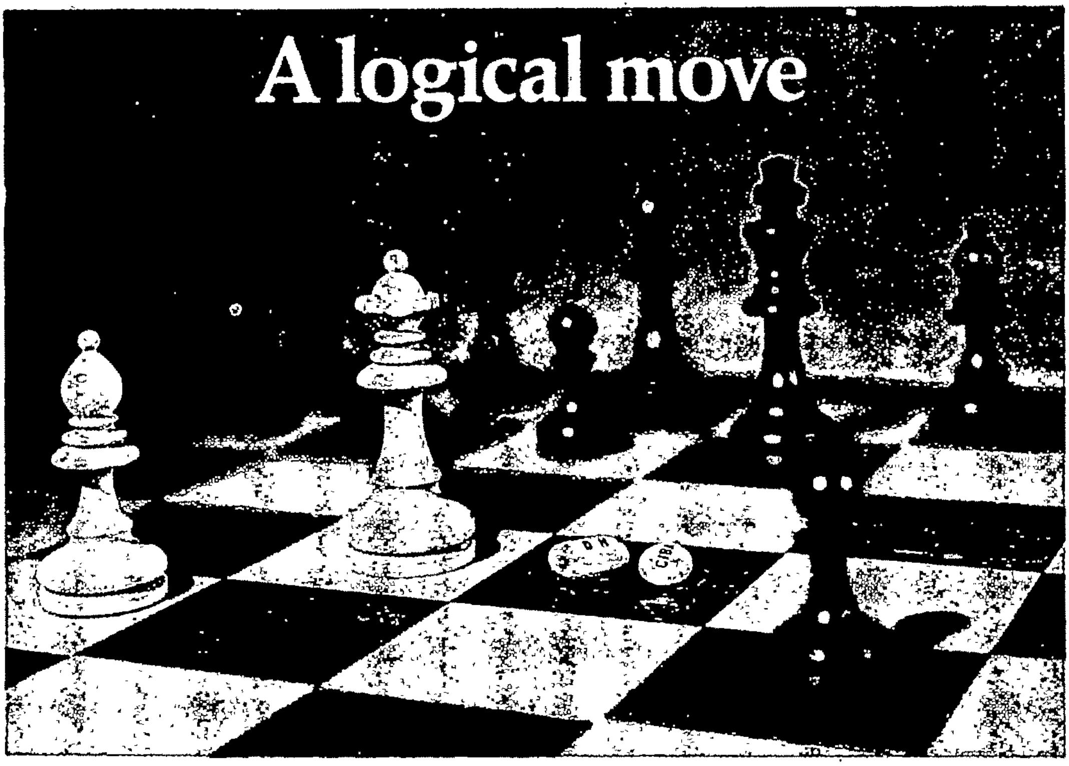

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Br. J. Dis. Chest (1979) 73, 211

Review Article

RESPIRATORY FUNCTION AND CARDIORESPIRATORY RESPONSE TO EXERCISE IN OBESITY

M. J. B. FAREBROTHER

Department of Medicine, St Thomas's Hospital Medical School, London

An association between obesity and breathlessness at rest or on exertion has long been recognized (Fothergill 1781). Physicians are aware of this and generally advise loss of weight for fat people who are breathless, whether the breathlessness is secondary to heart or lung disease or thought to be a result of the obesity itself. After much research over the last 20 years it is now recognized that there are many ways in which obesity can affect the function of the lungs. This article reviews these effects of obesity on lung function at rest and on the cardiorespiratory response to exercise, in subjects without heart or lung disease, and the improvements which occur with weight loss.

Obesity is a common and usually easily recognized condition, but a generally accepted definition is still lacking (Butterfield 1975). Attempts at the definition of obesity as a disease or pathological condition are normally based on finding a weight at which morbidity or mortality is increased above that for subjects of lesser weight. Ideal weight for each sex and height is defined as the weight associated with the least mortality in life insurance practice (Metropolitan Life Insurance Company 1959) and is usually given for three categories of body frame, small, medium and large. The greater the excess of weight over their ideal the greater the mortality (Society of Actuaries 1959). The mean (average) weight of a population in a Western (developed) country is greater than the ideal.

For practical purposes three weight ranges are easily recognized:

1. Subjects who on cursory external examination do not appear fat. This range will include those of near ideal weight and those of near average weight for each sex and height. In this review these subjects are called normal.
2. Subjects who appear fat. This range corresponds roughly with weight at least 30% in excess of ideal. These subjects are called obese in this review.
3. Subjects who appear very fat. This range corresponds roughly with weight at least 70% in excess of ideal. These subjects are called grossly obese in this review.

The various authors whose work is referred to have their own definitions of obesity, but the terms normal, obese and grossly obese will be used where possible in this review to guide the reader. Although the review is about the effects of obesity, some relevant evidence is given about the effects on respiratory function of weight and weight changes in subjects in the normal weight range.

The effects of obesity on respiratory function will be discussed under four main headings:

1. Effects on the control of respiration.
2. Effects on respiratory mechanics and lung volumes.

3. Effects on gas exchange.
4. Effects on the cardiorespiratory response to exercise.

EFFECTS OF OBESITY ON RESPIRATORY CONTROL

The majority of obese and grossly obese subjects maintain a normal arterial carbon dioxide pressure ($P\text{a}CO_2$) at rest (Alexander et al. 1962). When the $P\text{a}CO_2$ at rest is normal, the majority show a normal ventilatory response to inhaled carbon dioxide (Cullen & Formel 1962; Pevny & Scheida 1968) but in some this ventilatory response is less than in controls of normal weight (Gilbert et al. 1961). Hypoxic ventilatory drive is also normal in grossly obese subjects with normal $P\text{a}CO_2$ (Kronenberg et al. 1975).

A generalized reduction of alveolar ventilation relative to metabolic CO_2 production results in an increase of alveolar CO_2 pressure and hence an increased $P\text{a}CO_2$. Alveolar underventilation is defined as an increase of $P\text{a}CO_2$ above the normal range; a decreased alveolar and hence arterial oxygen pressure ($P\text{a}O_2$) also results from a decrease of alveolar ventilation. Alveolar underventilation as defined by a raised $P\text{a}CO_2$ at rest has been estimated to occur in about 10% of grossly obese subjects (Alexander et al. 1962). In my personal experience the incidence in young subjects with gross obesity not complicated by heart or lung disease is less than this.

The syndrome of gross obesity, somnolence, periodic breathing, cyanosis, right heart failure, raised $P\text{a}CO_2$ and polycythaemia is commonly called the 'Pickwickian syndrome' (Burwell et al. 1956) in honour of the fat boy Joe in Dickens' *Pickwick Papers* who displayed some of those features. Simpson (1958) pointed out that the first good clinical descriptions of the syndrome were those of Fothergill (1781). Fothergill described two patients and clearly understood that gross obesity was the cause of their disability; one was cured with weight loss. The syndrome is better called the 'underventilation syndrome of gross obesity' or the 'obesity hypoventilation syndrome' (Rochester & Enson 1974). Case reports have been reviewed by Auchinloss and Gilbert (1959) and Ward and Kelsey (1962).

In this underventilation syndrome the increased resting $P\text{a}CO_2$ is accompanied as expected by a reduced ventilatory response to inhaled CO_2 (Lyons & Huang 1968; Zwillich et al. 1975). Some of these subjects have significant hypoxic ventilatory drive and hence ventilation is reduced on changing from air to oxygen breathing (Leiner et al. 1967); but hypoxic ventilatory drive may be decreased (Zwillich et al. 1975) and one patient described had absent hypoxic ventilatory drive in the presence of a normal CO_2 response (Kronenberg et al. 1977). Subjects with the alveolar underventilation syndrome of gross obesity may be very sensitive to respiratory depressants (Weil & Prasad 1957) as in alveolar underventilation in the presence of airflow obstruction. The ventilatory response to inhaled CO_2 is increased and the $P\text{a}CO_2$ reduced by progesterone (Lyons & Huang 1968).

An obvious cause of alveolar underventilation in gross obesity is mechanical embarrassment of the lung by the mass of fat in the chest wall and abdomen. There is no close relationship between body weight and impaired ventilatory response to CO_2 (Gilbert et al. 1961); but abdominal binding in normal subjects increases the rise of $P\text{a}CO_2$ during 5% CO_2 breathing (Hackney et al. 1959) and in obese and grossly obese subjects resting $P\text{a}CO_2$ is related to the oxygen cost of increased ventilation (Kaufman et al. 1959). As only some grossly obese subjects underventilate and as alveolar ventilation may return to normal with relatively little weight loss (Burwell et al. 1956; Rochester & Enson 1974) there is probably a critical weight at which the mass of fat will cause underventilation which in the majority is never reached. The mass of fat needed to cause underventilation must depend on inherited or acquired characteristics of the respiratory control mechanism in each individual, in a similar way to the individual variation of ventilatory response to severe airflow obstruction (Lane et al. 1968).

Somnolence in obese subjects is not always caused by a raised $P\mathrm{aco}_2$. Recurrent arousal from sleep during the night with drowsiness due to sleep deprivation may be caused by upper airway obstruction because of apposition of the tongue and posterior pharyngeal wall each time the subject falls asleep (Gastaut et al. 1966; Walsh et al. 1972). The resting $P\mathrm{aco}_2$ and the ventilatory response to inhaled CO_2 are usually normal. These subjects may be improved by weight loss or permanent tracheostomy (Walsh et al. 1972; Kryger et al. 1974).

The underventilation syndrome of gross obesity is hazardous and sudden or unexpected death from pulmonary embolism, CO_2 narcosis or upper airway obstruction is frequent (MacGregor et al. 1970; Miller & Granada 1974; Hasan et al. 1976).

The rest of this review is mainly concerned with the majority of obese and grossly obese subjects who maintain a normal alveolar ventilation and $P\mathrm{aco}_2$.

EFFECTS OF OBESITY ON RESPIRATORY MECHANICS AND LUNG VOLUMES

As would be expected, an increased mass of fat in the chest wall and abdomen has an effect on the mechanical properties of the chest wall and diaphragm, in turn leading to an altered movement of them during inspiration and expiration and therefore changes of lung volumes and the overall and regional pattern of ventilation.

Compared with normals, the compliance of the respiratory system (that is the change of volume per unit change of pressure) is decreased in obese and grossly obese subjects (Safar & Aguto-Escarraga 1959; Waltemath & Bergman 1974). The compliance of the chest wall is more reduced than the compliance of the lungs (Naimark & Cherniack 1960). The work of breathing, estimated as the oxygen cost of increased ventilation, is increased in many obese subjects, but normal in some (Kaufman et al. 1959; Gilbert et al. 1961; Cullen & Formel 1962). During ventilation both elastic ('stored') and non-elastic ('wasted') work are greater in obese subjects than in normals (Bosman & Goldman 1961). The muscular activity of the diaphragm, estimated from the diaphragmatic electromyogram, is increased in grossly obese subjects (Lourenco 1969). The efficiency of the respiratory muscles, that is the mechanical work output per unit O_2 uptake, is less in obese subjects than in those of normal weight (Fritts et al. 1959; Cherniack & Guenter 1961).

Resting tidal volume (VT) is reduced in obese subjects (Kaufman et al. 1959; Said 1960; Cherniack & Guenter 1961) and respiratory frequency (fr) is correspondingly increased. Work of breathing against an elastic resistance increases with increase of VT and spontaneous levels of VT are often those associated with least work, despite the increased dead space ventilation this must entail (Otis 1954; Fishman et al. 1957).

Many studies of lung volumes in obesity are difficult to interpret because the obese subjects are compared with predictions based on normal populations which may not be representative of the population from which the obese subjects under study are drawn.

The most reliable have used their own normal weight control subjects. Typical differences of lung volumes in obese subjects from those in normal subjects, with the effects of posture and weight loss, are illustrated in Fig. 1 (Farebrother 1977).

Vital capacity (VC) is decreased in some but not all obese and grossly obese subjects (Bowen 1923; Burwell et al. 1956; Bedell et al. 1958). Expiratory reserve volume (ERV) is consistently reduced in obese subjects (Sieker et al. 1955; Burwell et al. 1956; Bedell et al. 1958; Gilbert et al. 1961; Cullen & Formel 1962). Tucker and Sieker (1960) compared 13 grossly obese subjects (mean weight 130 kg) with nine subjects of near normal weight previously studied in the same laboratory (Blair & Hickam 1955); mean VC was 37% less in the obese than in the normals and mean ERV was 67% less. In 48 grossly obese preoperative patients, Vaughan and Wise (1975*a*) found mean ERV 56% of predicted.

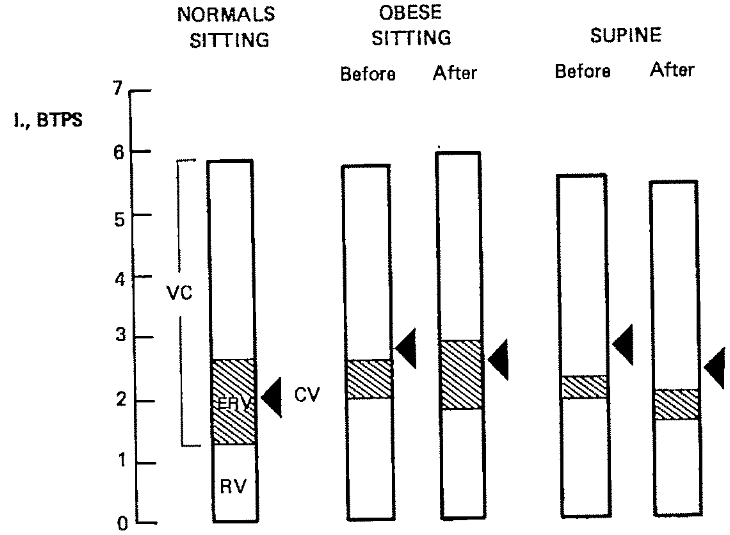

Fig. 1. Lung volumes and closing volume in eight obese subjects in the sitting and the supine posture, before and after weight loss, and in eight matched controls of normal weight. (*From Farebrother 1977*)

Evidence about differences of residual volume (RV) between normals and obese subjects is conflicting; some studies show an increase in obesity, some a decrease, but most no significant difference. In one of the best investigations (Tucker & Sieker 1960) mean RV was greater in obese subjects than in normals but the difference was not statistically significant. Farebrother (1977) (Fig. 1) found mean RV significantly greater in eight grossly obese subjects than in controls, but the obese subjects smoked many more cigarettes than the controls and this may have been the cause of the difference. Total lung capacity (TLC) and functional residual capacity (FRC) are often decreased in obesity because of reduction of VC and ERV respectively, and the decrease of FRC has also been demonstrated by body plethysmography (Emirgil & Sobol 1973).

In subjects of near normal weight a change from the sitting to the supine posture is accompanied by a decrease of VC and by a larger decrease of ERV (Wilson 1927;

Hurtado & Fray 1933; McMichael & McGibbon 1939). In the supine posture VC and ERV in grossly obese subjects remains less than in normal subjects by the same proportion as in the sitting posture (Tucker & Sieker 1960).

In obese and grossly obese subjects VC is linearly correlated with the total compliance of the respiratory system (Naimark & Cherniack 1960; Sharp et al. 1964*a*) which is in turn negatively correlated with weight (as a percentage of ideal) (Naimark & Cherniack 1960). In contrast to normals, change of posture from sitting to supine decreases chest wall compliance in the obese (Naimark & Cherniack 1960).

Vital capacity of obese subjects tends to increase with loss of weight (Bowen 1923; Master et al. 1942; Bedell et al. 1958) even when near normal before weight loss (Emirgil & Sobol 1973; Kronenberg et al. 1975). Increase of ERV with weight loss is greater (Bedell et al. 1958; Barrera et al. 1967). In a series of 10 grossly obese subjects who lost weight (MacKenzie et al. 1969) ERV increased in all and further examination of their results shows a roughly linear relationship between amount of weight lost and increase of ERV. Even with considerable weight loss, however, there may be little increase of ERV in the supine posture (Farebrother et al. 1974; Sixt et al. 1976). Most series have found no consistent change of RV following weight loss. Farebrother (1977) found that in eight grossly obese subjects mean RV did decrease with substantial weight loss and the decrease was greater in the supine posture (Fig. 1). ERV seems to be the partition of lung volume most sensitive to weight change; it is negatively correlated with body weight even in a population of normal weight distribution (Needham et al. 1954) and may be affected by small weight gains and losses in subjects of near normal weight (Cotes & Gilson 1967).

The lung volume point below which the normal pattern of ventilation is reversed, so that there is more ventilation of uppermost than lowermost lung zones, can be detected using boluses of tracer gas (Dollfuss et al. 1967). The volume from this point to the end of full vital capacity expiration has been called the closing volume (CV) and may be considered an estimate of the lung volume at which small airways begin to close in dependent lung regions (Collins 1973). CV/VC% may be greater in grossly obese subjects than in normals (Farebrother et al. 1974), possibly related to smoking (Sixt et al. 1976), but more likely due to decrease of VC rather than increase of CV in some of these subjects. With weight loss there was a significant decrease of CV/VC% in the subjects of Sixt et al. (1976) due to the increase of VC; CV remained the same. CV may be added to RV to give the point of onset of airway closure in terms of absolute lung volume, the closing capacity (CC). Farebrother (1977) showed CV to be the same in obese as in normal subjects, but CC was increased in the obese because of greater RV (Fig. 1). In the supine posture CC was less after weight loss than before because in this posture RV became less with weight loss. Neither this author nor Sixt et al. (1976) found much change of CC with weight loss in the sitting posture.

Residual volume may be determined by the end of a process of rising closure of small airways during expiration, at least in dependent lung regions (Cotes 1975), the same process of which CC represents the beginning. It is therefore of interest that RV and CC appear to change together in conditions of increased chest wall and abdominal mass altering pleural and intra-abdominal pressure.

Most of the changes of respiratory mechanics and lung volumes seen in obese subjects can be reproduced by strapping or binding the chest or abdomen (Hackney et al. 1959; Caro et al. 1960), wearing a G-suit (Cherniack & Guenter 1961) or mass loading the lower chest or upper abdomen (Waltemath & Bergman 1974). Mass loading of the respiratory system by placing weights on the lower chest decreases compliance in normals more than upper chest loading, but obese subjects with alveolar underventilation have changes which more resemble those of abdominal mass loading, or elastic loading of the thorax (Sharp et al. 1964*b*).

EFFECTS OF OBESITY ON GAS EXCHANGE

Hypoxaemia in obesity

Although a low $P\mathrm{a}O_2$ whilst breathing air is an essential accompaniment of a raised $P\mathrm{a}CO_2$ in obese subjects with alveolar underventilation, hypoxaemia is also common in the majority of obese and grossly obese subjects in whom $P\mathrm{a}CO_2$ and overall alveolar ventilation are normal (Said 1960; Barrera et al. 1967; Lourenco 1969; Emirgil & Sobol 1973; Farebrother et al. 1974). In 48 grossly obese subjects in the upright posture mean $P\mathrm{a}O_2$ was 10.0 kPa (75 mmHg) (Vaughan & Wise 1975*a*). The remainder of this discussion of the impairment of pulmonary gas exchange and its causes in obesity is confined to obese subjects with a resting $P\mathrm{a}CO_2$ within the normal range.

An estimate of the degree of impairment of oxygen transfer from alveolar gas to arterial blood can be made by calculating the 'ideal' alveolar oxygen pressure ($P\mathrm{A}O_2$) using the ideal alveolar air equation and hence determining the alveolar to arterial oxygen pressure difference ($P\mathrm{A}$–$\mathrm{a}O_2$) (Riley et al. 1946, 1951). In this analysis all alveoli which are ventilated and perfused are assumed to be equally ventilated and perfused. The $P\mathrm{A}$–$\mathrm{a}O_2$ is then due either to failure of equilibration of oxygen between alveolar gas and blood at the end of the pulmonary capillary (now thought to be unlikely breathing air at rest close to sea level) or to blood flow through unventilated alveoli. In reality part of the $P\mathrm{A}$–$\mathrm{a}O_2$ is attributable to blood flow through relatively underventilated alveoli, that is alveoli with a low ventilation to perfusion ratio. During 100% O_2 breathing such alveoli no longer contribute to the $P\mathrm{A}$–$\mathrm{a}O_2$, which is then entirely attributable to blood flow through unventilated alveoli and to any true (anatomical) right to left blood shunt. As expected, $P\mathrm{A}$–$\mathrm{a}O_2$ is increased in obese subjects with low $P\mathrm{a}O_2$ and without overall underventilation (Said 1960) and in 12 obese subjects in the supine posture mean $P\mathrm{A}$–$\mathrm{a}O_2$ remained greater than in normals during O_2 breathing, showing that some of the increase of $P\mathrm{A}$–$\mathrm{a}O_2$ while breathing air is attributable to blood flow through unventilated alveoli (Said & Banerjee 1963). In six of these subjects $P\mathrm{A}$–$\mathrm{a}O_2$ while breathing oxygen could be reduced by taking four deep breaths, suggesting that some of these alveoli are ventilated at higher lung volumes.

$P\mathrm{a}O_2$ was less in the supine than in the sitting posture in four out of five obese subjects (Said 1960) and Farebrother et al. (1974) demonstrated a significant decrease of $P\mathrm{a}O_2$ on changing from the sitting to the supine posture in eight grossly obese subjects (mean weight 120 kg), a mean decrease of 1.07 kPa (8 mmHg) before and 1.60 kPa (12 mmHg) after weight loss (mean weight 86 kg). In contrast Vaughan et al. (1974) found no significant difference between $P\mathrm{a}O_2$ in the sitting posture and in the supine posture in 20 grossly obese subjects of mean weight 144 kg or between the semi-recumbent and supine postures in 22 grossly obese subjects of mean weight 138 kg (Vaughan & Wise 1975*b*), although $P\mathrm{a}O_2$ in all three postures was significantly less than normal. Paul et al. (1976)

showed that cardiac output and venous admixture (shunt effect) were greater supine than sitting in grossly obese subjects during O_2 breathing.

$Pa{O_2}$ may increase with weight loss (Barrera et al. 1967; Emirgil & Sobol 1973; Jacobsen et al. 1974; Kronenberg et al. 1975). Only six of the eight subjects of Farebrother et al. (1974) showed an increase in $Pa{O_2}$ with substantial weight loss and the mean increases were not statistically significant in either the sitting or supine posture.

Sixt et al. (1976) demonstrated a significant increase of $Pa{O_2}$ and decrease of $P{A\text{–}aO_2}$ with weight loss in both the sitting and the supine postures in 12 obese subjects. In one series (Farebrother et al. 1974) there was some evidence of improvement of oxygen transfer only when weight had been lost to relatively near ideal, but in other series substantial weight loss was accompanied by an increase of $Pa{O_2}$ in some subjects who still remained very obese (Barrera et al. 1967; Emirgil & Sobol 1973; Kronenberg et al. 1975; Chodoff et al. 1977).

Distribution of pulmonary ventilation and blood flow and relationships to gas exchange

Barrera et al. (1969) investigated the relationship of ventilation distribution to gas exchange in obese and grossly obese subjects by dividing alveolar volume into better and less well ventilated compartments using nitrogen and helium wash-in and wash-out curves. They assumed that blood flow was distributed in proportion to the volume of these compartments. In some subjects the less well ventilated compartment had more blood flow than this compartment in subjects of near normal weight. In some others persistence of hypoxaemia during O_2 breathing indicated a blood shunt bypassing the lungs or passing through completely unventilated lung regions; the authors suggest that they had areas of collapsed unventilated alveoli. Both these effects would contribute to hypoxaemia whilst breathing air. An extension of this study (Barrera et al. 1973) with fewer assumptions came to a similar conclusion.

Said (1960) had hypothesized that hypoxaemia in obesity is caused by rapid shallow breathing at low lung volumes, associated with airway closure and regional atelectasis. Certainly $Pa{O_2}$ in grossly obese subjects may be increased by taking a few deep breaths (Said & Banerjee 1963; Rørvik & Bø 1976). Holley et al. (1976) were the first to investigate the regional distribution of ventilation and blood flow in the lungs of obese and grossly obese subjects in the sitting posture using Xenon 133. In four of eight subjects the normal pattern of ventilation was reversed, so that a resting inspiration from FRC was distributed more to the upper than to the lower lung zones. The lower regions therefore had a reduced ventilation to blood flow ratio which might lead to hypoxaemia, but the blood gas data were incomplete and the connection was not demonstrated. The reversal of the ventilation pattern occurred in the four subjects with smallest ERV. George and Weill (1971) found the same reversal of the pattern of ventilation in some obese subjects when they investigated the pattern of regional expansion of the lungs by measuring changes of density to X-rays (fluorodensitometry).

When closing volume (CV) exceeds ERV (that is when closing capacity (CC) exceeds FRC) there is closure of small airways in dependent lung regions during resting tidal breathing, leading to underventilation of these dependent zones. This should lead to an increase of the admixture of relatively unoxygenated blood to the arterial blood, and excess of CV over ERV (that is, negative values of (ERV – CV)) is related to increase of $P{A\text{–}aO_2}$ in normal subjects in both the sitting and the supine postures (Craig et al. 1971*a*).

Expressing (ERV – CV) as a proportion of VC, (ERV – CV)/VC%, Farebrother et al. (1974) found that in eight grossly obese subjects there was evidence of airway closure during resting tidal breathing in six sitting and in all eight supine before weight loss and in four sitting and six supine after weight loss. The improvement in the mean value of (ERV – CV)/VC% with weight loss was significant for the sitting posture only. $P\text{ao}_2$ (Farebrother et al. 1974) and $P\text{A–ao}_2$ (McHardy et al. 1975; Sixt et al. 1976; Hedenstierna et al. 1976) are significantly correlated with (ERV – CV)/VC% or (FRC – CC) (Fig. 2).

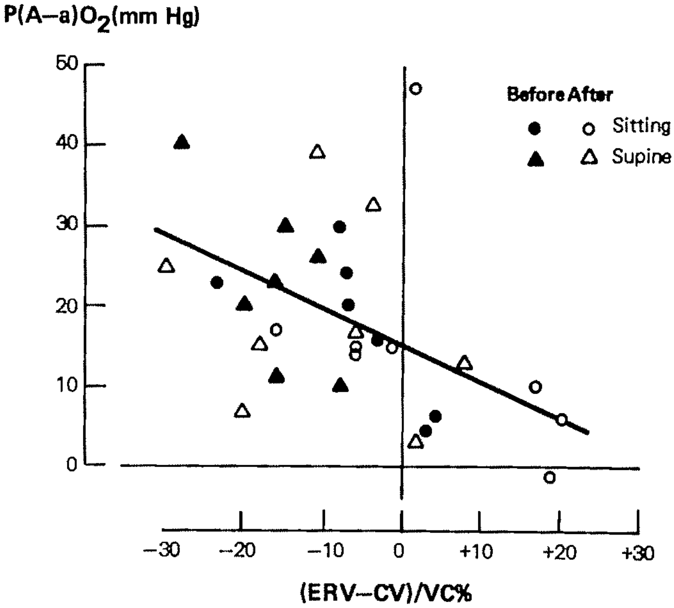

Fig. 2. The relationship between $P\text{A–ao}_2$ and (ERV – CV)/VC% in the sitting and supine posture before and after weight loss in eight obese subjects. The regression line of closest fit for all the points as shown is $P\text{A–ao}_2 = 15.5 - 0.44$ [(ERV – CV)/VC%] SD ± 10 mmHg ($P < 0.01$). (*From McHardy et al. 1975*)

Underventilation of dependent lung regions with normal blood flow, because of reduced ERV and breathing near to RV so that there is small airway closure during resting tidal breathing, is thus established as the cause of hypoxaemia in obese subjects with normal $P\text{aco}_2$.

In subjects of normal weight Craig et al. (1971*a*) found that $P\text{A–ao}_2$ is greater supine than sitting when CV exceeds ERV in the supine but not in the sitting posture, but when CV exceeds ERV in both postures there is no change, $P\text{A–ao}_2$ being increased in both postures. This latter situation is most likely in the most grossly obese. The discrepancy between the postural difference of $P\text{ao}_2$ found by Farebrother et al. (1974) and the lack of difference of $P\text{ao}_2$ or $P\text{A–ao}_2$ found by the others (Vaughan et al. 1974; Vaughan & Wise 1975*b*; Paul et al. 1976) may be attributable to the difference of mean weight of the subjects, 120 kg in the former case and 144 kg, 138 kg, and 138 kg respectively in the latter cases.

Hypoxaemia in conditions analogous to obesity

It has long been known that breathing close to RV may impair gas exchange (Haldane et al. 1919). It is now known that there are many conditions where gas exchange may be impaired because of relative underventilation of dependent lung regions because of airway closure within the range of tidal breathing because of increase of CV (CC) or decrease of ERV (FRC) or both. In many of these conditions the evidence for relationship between airway closure and impairment of gas exchange is incomplete. Known changes in those conditions which are analogous to obesity, with reduction of ERV, are summarized in Table I.

Table I. Summary of known changes of end expiratory lung volume, closing volume and indices of gas exchange, and their relationship, in conditions where gas exchange may be disturbed associated with a reduction of ERV*

	Change of ERV or FRC	*Change of CV or CC*	*Change of* $P\mathrm{a}_{O_2}$ *or* $P_{A}\text{–}\mathrm{a}_{O_2}$	$P\mathrm{a}_{O_2}$, $P_{A}\text{–}\mathrm{a}_{O_2}$ *or* $C(c'\text{–}a)_{O_2}$ *related to* $(ERV-CV)$
Supine posture (compared to sitting)	ERV↓ FRC↓	Little or no change	$P\mathrm{a}_{O_2}$↓ in older subjects	Yes
Old age (compared to younger)	ERV↓ FRC same	CV↑ CC↑	$P\mathrm{a}_{O_2}$↓ more in supine posture	Yes
Chest, or chest and abdomen compression				
Chest strapping	ERV↓ FRC↓	CC↓	$P\mathrm{a}_{O_2}$↓	
Water immersion	ERV↓ FRC↓		$P\mathrm{a}_{O_2}$↓	
Altered abdominal mechanics				
Pregnancy	ERV↓ FRC↓		$P\mathrm{a}_{O_2}$↓ supine	
Pneumoperitoneum	ERV↓ FRC↓			
Ascites	ERV↓ FRC↓			
Peritoneal dialysis			$P\mathrm{a}_{O_2}$↓	
After hemicorporectomy	ERV↓ FRC↓	CV > ERV	$P_{A}\text{–}\mathrm{a}_{O_2}$↑	
After laparotomy	ERV↓ FRC↓	CV > ERV	$P\mathrm{a}_{O_2}$↓ $P_{A}\text{–}\mathrm{a}_{O_2}$↑	Yes
Obesity	ERV↓ FRC↓	CV unchanged or ↑	$P\mathrm{a}_{O_2}$↓ $P_{A}\text{–}\mathrm{a}_{O_2}$↑	Yes

* Conditions where pathological changes within the lungs lead to disturbance of gas exchange by an increase of CV, such as early chronic bronchitis and left heart failure, are not included.

As already noted, ERV is less in the supine than in upright postures in normal subjects. CV and CC increase with age (Buist & Ross 1973), but there is little difference of CV between the sitting and supine postures (Leblanc et al. 1970; Collins et al. 1973). As a result of these changes CV exceeds ERV at an earlier age in the supine than in the sitting posture (Leblanc et al. 1970; Craig et al. 1971*b*). $P\text{ao}_2$ decreases with increasing age (Raine & Bishop 1963) more in the supine (Sorbini et al. 1968) than in the sitting posture (Mellemgaard 1966); there is no postural difference of $P\text{ao}_2$ in young non-smokers (Strieder et al. 1969; Ang et al. 1969) but $P\text{ao}_2$ is significantly less supine than sitting in elderly subjects (Ward et al. 1966). Craig et al. (1971*a*) related (ERV – CV) to $P\text{A–ao}_2$ in normal subjects.

In grossly obese subjects there is embarrassment of the thorax from the fat on the chest wall and in the abdomen. It might be expected that there would be similarities with other circumstances where there is restriction of chest wall movement. With strapping of the chest or abdomen ERV, RV and VC are all reduced (Caro et al. 1960); this is associated with a decrease of $P\text{ao}_2$ (McIlroy et al. 1962), which might be due to airway closure in the range of tidal breathing. Strapping of the chest also leads to a decrease of CC/TLC% (Sybrecht et al. 1975), a difference from obese subjects. Immersion in water also places an encumbrance on chest wall movement. Water immersion is known to cause reduction of ERV (Hong et al. 1960) and RV (Agostoni et al. 1966); there is evidence of air trapping at FRC (Dählbeck & Lundgren 1972) probably due to airway closure, although this has not been demonstrated. Water immersion reduces $P\text{ao}_2$ and increases $P\text{A–ao}_2$ (Cohen et al. 1971).

The obese can also be compared with other subjects with abdominal swelling which might have a similar mechanical effect on the diaphragm and rib cage. Reduction of ERV and RV has been shown in pneumoperitoneum (Wright et al. 1949; Patton et al. 1953), ascites (Abelmann et al. 1954) and pregnancy (Cugell et al. 1953; Gee et al. 1967). In late pregnancy $P\text{ao}_2$ is significantly lower in the supine than in the sitting posture (Ang et al. 1969). Evidence of airway closure in the range of tidal breathing in later pregnancy has been put forward (Bevan et al. 1974), but this study showed no difference of (ERV – CV) between the sitting and the supine posture, and so would not account for the postural difference of $P\text{ao}_2$. Obese pregnant subjects have decreased $P\text{ao}_2$ in the sitting posture but there is little difference between the pregnant and post-partum $P\text{ao}_2$ (Eng et al. 1975), so the effects of obesity and pregnancy may not be additive. During peritoneal dialysis, an iatrogenic ascites, there is a fall of $P\text{ao}_2$ on running the fluid into the abdomen, greater with a larger volume of fluid, and $P\text{ao}_2$ promptly recovers on running out the fluid (Goggin & Joekes 1971); this is likely to be due to changes of FRC relative to CC during the cycle (Freedman & Maberly 1971). In one subject following hemicorporectomy, an amputation of the lower half of the body just above the pelvic girdle, abdominal mechanics were altered with reduction of RV and ERV, CV exceeding ERV, and a $P\text{A–ao}_2$ at rest greater than predicted (Bake & Grimby 1974).

Another condition altering abdominal mechanics, abdominal surgery, has been better studied, although the situation is less obviously analogous to that of obese subjects. For several days after laparotomy ERV and RV are reduced (Beecher 1933) and the reduction of ERV is accompanied by a reduction of $P\text{ao}_2$ (Palmer & Gardiner 1964; Lewis & Welch 1965), and a corresponding increase of $P\text{A–ao}_2$ (Palmer et al. 1965; Alexander et al. 1973). Alexander et al. (1973) also demonstrated an inverse relationship of $P\text{A–ao}_2$ and (ERV – CV) for all their observations pooled. The postoperative fall of FRC and other lung volumes is thought to be due to pain restricting the movement of abdominal muscles, hence restricting diaphragmatic movement. In grossly obese subjects, in whom $P\text{ao}_2$ is already low, $P\text{ao}_2$ may fall further during operation (Tsueda et al. 1976) or postoperatively

(Vaughan et al. 1974). The fall of $Pa\text{O}_2$ lasts about five days, is greater in the supine than in a semirecumbent position (Vaughan & Wise 1975*b*) and lasts less long after a transverse than after a vertical upper abdominal incision (Vaughan & Wise 1975*a*).

Although $Pa\text{O}_2$ in healthy young obese subjects even in the supine posture (Farebrother et al. 1974; Sixt et al. 1976) is not sufficiently low for major desaturation of arterial blood, it is apparent that obesity may contribute to important hypoxaemia in the presence of other factors such as old age, recumbent posture and abdominal surgery. Smoking (McCarthy et al. 1972; Buist et al. 1973) and fluid overloading of the lungs due to left heart disease (Collins et al. 1975), chronic renal failure (Stanescu et al. 1974) or hepatic cirrhosis (Ruff et al. 1971) may all increase CV and further exacerbate the hypoxaemia.

EFFECTS OF OBESITY ON CARDIORESPIRATORY RESPONSE TO EXERCISE

Fothergill (1781) recognized that gross obesity may be associated with an abnormal degree of exertional dyspnoea, and that a good exercise tolerance may be restored by weight loss. Many grossly obese subjects say when asked that they are short of breath on exertion (Alexander et al. 1962).

Oxygen uptake ($\dot{V}\text{O}_2$) at rest is increased in obese subjects linearly with the increase of weight (White & Alexander 1965; Bray et al. 1970) but the ratio of $\dot{V}\text{O}_2$ to body surface area is normal (White & Alexander 1965). $\dot{V}\text{O}_2$ is greater in obese subjects than in subjects of normal weight, and $\dot{V}\text{O}_2$ is linearly related to body weight, during treadmill exercise (Seltzer 1940; Mahadeva et al. 1953; Miller & Blyth 1955; Auchinloss et al. 1963; Cotes 1969), stepping exercise (Mahadeva et al. 1953; Cotes 1969; Godin & Shephard 1973), outdoor bicycle riding (Adams 1967) and a wide range of other activities (Malhotra et al. 1962). $\dot{V}\text{O}_2$ during treadmill exercise is increased by small weight gains (Cotes & Gilson 1967; Durnin & Norgan 1969; Hanson 1973) and the effect of increased body weight can be reproduced by a weighted back-pack (Goldman & Iampetro 1962; Turell et al. 1964; Hanson 1973). Maximal $\dot{V}\text{O}_2$ is correlated with body weight but better correlated with fat-free weight (Buskirk & Taylor 1957), but because of work done in moving the body weight this increased maximal $\dot{V}\text{O}_2$ in the obese is reached at a lower treadmill speed and grade than the lower maximal $\dot{V}\text{O}_2$ of subjects of normal weight.

During exercise on a bicycle ergometer at moderate work loads, $\dot{V}\text{O}_2$ is again greater in obese and grossly obese subjects than in normals (Astrand et al. 1960), and some authors have found that the difference of $\dot{V}\text{O}_2$ between obese subjects and normals was the same at all work loads (Dempsey et al. 1966*b*; Bray et al. 1977); but Davies et al. (1975) demonstrated that in young female subjects the slope of the relationship of $\dot{V}\text{O}_2$ to external work load was also greater in obese subjects than in those of normal weight. $\dot{V}\text{O}_2$ during bicycle exercise is increased in obese subjects mainly because of the increased work of moving the weight of the legs in a vertical direction. Adding weights to the legs of normal subjects during bicycle exercise increases $\dot{V}\text{O}_2$ (Kamon et al. 1973) and at a fixed pedalling frequency $\dot{V}\text{O}_2$ is linearly related to body weight even at zero work load (Wasserman & Whipp 1975). During treadmill exercise, the rate of increase of ventilation (and therefore presumably of $\dot{V}\text{O}_2$) with increasing added loads is much greater for foot loads than for loads carried on the back (Draper et al. 1953), probably because of the greater vertical distance moved by the legs than by the trunk while walking. Godin and Shephard (1973) have proposed that the net oxygen cost of an activity (that is the increase over resting) is proportional to a power of the body weight, that is net $\dot{V}O_2 \propto (Wt)^b$; b approaches one for activities with extensive body movement and b approaches zero for activities with little body movement. The penalty of obesity in terms of exertional dyspnoea and limitation of exercise tolerance is thus greatest when body movement is a large proportion of the total work done in completing a task, a conclusion which common sense would suggest.

The efficiency of muscular work can be defined as the mechanical work output divided by the increment of energy expenditure (derived from the increment of $\dot{V}O_2$) over resting to achieve it. It has been claimed that muscular efficiency is reduced during bicycle exercises in obese and grossly obese subjects (Wang et al. 1930; Astrand et al. 1960) but this is not the case if the mechanical work of moving the legs is taken into account (Bray et al. 1977). Careful studies during treadmill exercise (Turell et al. 1964) and arm work (McKee & Bolinger 1960) have shown no difference of muscular efficiency between obese or grossly obese subjects and those of near normal weight, nor can any change of muscular efficiency be shown during bicycle exercise after a gain in weight (Whipp et al. 1973).

Differences of ventilation on exercise between obese subjects and those of near normal weight are in general in the same direction and to similar degree as those of $\dot{V}O_2$. There is, however, some evidence that a weight increase may slightly reduce the ventilatory response to exercise at standard $\dot{V}O_2$ (Cotes et al. 1969; Kollias et al. 1972; Hanson 1973). This is presumed to be a result of the increased work of breathing at the greater weights. For the same exercise ventilation obese subjects breathe faster and more shallowly than those of normal weight (Turell et al. 1964; Dempsey et al. 1966*a*).

For the same speed and grade on a treadmill, heart rate (fH) is positively correlated with body weight (Cotes 1969). The difference between resting and active (night and day) fH is also correlated with body weight (Richardson 1971). It might be thought that these relationships paralleled those of $\dot{V}O_2$ and weight under the same conditions, but when fH is measured at standard $\dot{V}O_2$ it is negatively correlated with body weight during walking exercise (Cotes 1969) and during normal daily activities of normal and obese schoolgirls (Bradfield et al. 1971). Cotes et al. (1969) showed that in male subjects of near normal weight the slope of the regression of fH on $\dot{V}O_2$ is less in heavier than in lighter subjects. In more obese subjects the slope of this relationship is negatively correlated with body weight (Farebrother 1977).

All the findings indicate an increased oxygen pulse in the obese (that is $\dot{V}O_2$ divided by fH, an estimate of oxygen uptake by the tissues with each heart beat). The oxygen pulse is also the product of the stroke volume and the arteriovenous oxygen content difference. It can therefore by inferred that one of these is increased in the obese. In view of the increased heart size with hypertrophied but otherwise normal myocardium at autopsy in the obese (Amad et al. 1965) an increase of stroke volume seems more likely.

In the context of the response to exercise, a 'fit' person is one in whom the increase of fH is economically low for a given increase of $\dot{V}O_2$ (Spiro et al. 1974). The relationship of fH to $\dot{V}O_2$ on exercise in obese subjects differs from that in subjects of normal weight in the same way as trained differ from untrained subjects (Ekblom et al. 1968). It could be considered that the obese are fitter, due to the training effect of carrying about the excess body weight, but this implies that the change is beneficial. It seems better to regard it as just appropriate to a condition of increased demand upon the myocardium.

CONCLUSIONS

The possible respiratory abnormalities in obesity and their inter-relationships are shown in Fig. 3. Alveolar underventilation is relatively uncommon even in gross obesity and may be improved with relatively little weight loss. Other obese and especially grossly obese subjects have altered chest wall mechanics leading to reduced lung volumes, especially ERV, small airway closure in the range of tidal breathing and arterial hypoxaemia. These changes are more marked in the supine posture except in the most grossly obese. These respiratory abnormalities are unlikely to do much immediate harm to young obese subjects without heart or lung disease and the main penalty in these subjects is the increased oxygen consumption and hence limitation of exercise tolerance during work in which the body weight is moved. Hypoxaemia in these subjects is not associated with major desaturation of arterial blood, but may be very important where obesity combines with other factors such as old age, lung disease, left heart failure, fluid overloading and abdominal surgery. Although the evidence is incomplete it is likely that weight loss would lessen hypoxaemia in these circumstances.

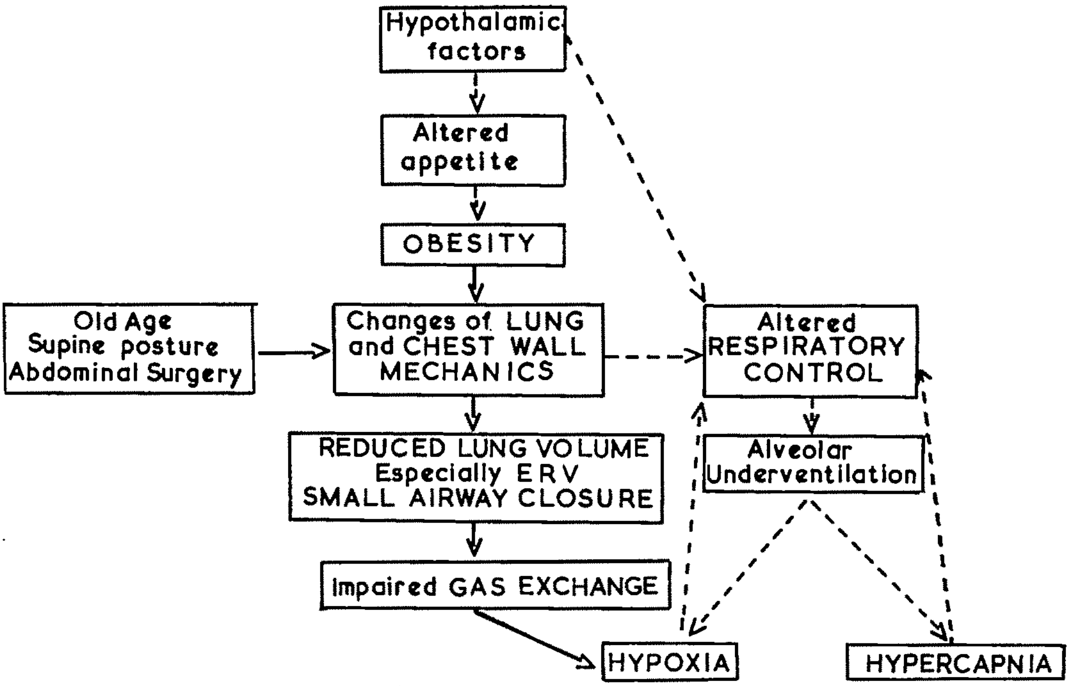

Fig. 3. Possible respiratory abnormalities in obesity and their inter-relationships. The relationships shown ——→ commonly occur, those shown – – – –→ less commonly occur

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RESPIRATORY ILLNESS, MATERNAL SMOKING HABIT AND LUNG FUNCTION IN CHILDREN

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Summary

Two hundred and fourteen children aged 7–11 years had tests of lung function performed. Mothers were asked about their past and current smoking habits and whether their children had ever had pneumonia or severe bronchitis. The findings suggest a relationship between early childhood bronchitis or pneumonia and impairment of lung function in later childhood and also suggest that maternal smoking habit may contribute directly to impairment of lung function in children.

INTRODUCTION

Previous studies (Lunn et al. 1967; Holland et al. 1969) have demonstrated a relationship between bronchitis and pneumonia in early childhood and impairment of lung function in later life. Other work (Colley et al. 1974) has shown that parental smoking can contribute to the development of respiratory illness in early childhood. The present paper explores the influence of these features on subsequent lung function in children.

Methods

In the course of a community study of respiratory function in relation to housing conditions 214 children aged 7–11 years were seen at school. Each child's lung function was measured by the use of a bellows spirometer; heights and weights were recorded. Each child's mother was interviewed at her home.

All lung function measurements were made during the summer months. The following lung function indices were calculated for each child from the spirometer tracings: the forced mid-expiratory flow (FMF); the forced expiratory volume in 0.75 of a second ($FEV_{0.75}$); the forced vital capacity (FVC). Statistical methods have been described in detail previously (Yarnell & St Leger 1977) but are summarized briefly below.

The lung function measurements were converted to height-standardized indices by use of the relationship: Derived index = LFT/Height^K, where LFT is the spirometric result for each index of lung function and for each child; the exponent K is a constant for each lung function index and for each sex. Values of K were calculated from pooled data from this study and are shown in Table I.

The values of the derived indices have been re-standardized to a height of 130 cm to facilitate comparison of results.

Table I. Values of exponent K estimated from pooled data

Lung function test	*Males*	*Females*
FMF	2.05	2.54
FEV$_{0.75}$	2.20	2.04
FVC	2.20	1.89

RESULTS

Fig. 1 shows the mean values of the lung function indices standardized to a height of 130 cm, according to the presence or absence of a history of bronchitis or pneumonia in each child. Children with a history of bronchitis or pneumonia have, on average, lower values for the lung function indices FMF and FEV$_{0.75}$ compared to children without such a history. Average FVC values are reduced to a lesser extent. The average reduction in FMF for boys is 9%; and for girls is 12%; the average reduction in FEV$_{0.75}$ for boys is 5%; and for girls is 7%.

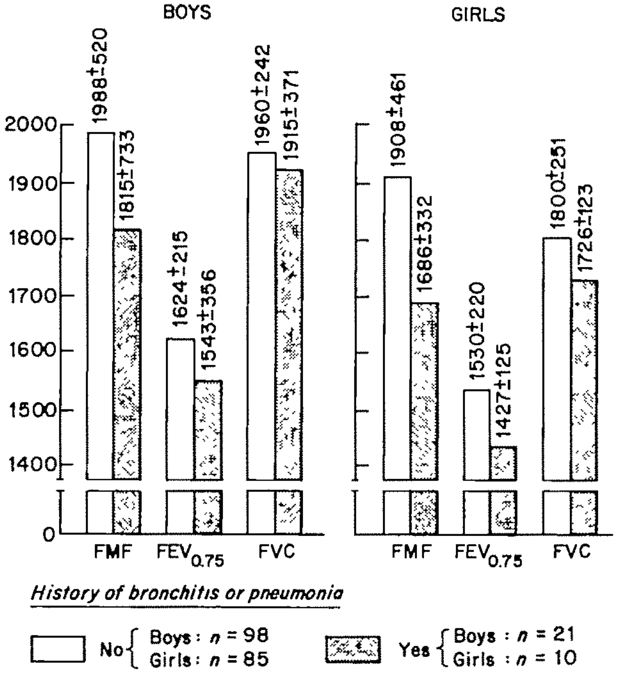

Fig. 1. Lung function and past history of chest infection (mean ± SD) standardized to height of 130 cm (FMF ml/sec; FEV$_{0.75}$ ml; FVC ml)

Table II shows the distribution of children with and without a history of bronchitis or pneumonia according to the smoking habit of their mothers in pregnancy. Fig. 2 shows that the offspring of mothers who reported that they had smoked more than 10 cigarettes daily throughout pregnancy had reduced lung function (FMF and FEV$_{0.75}$) compared

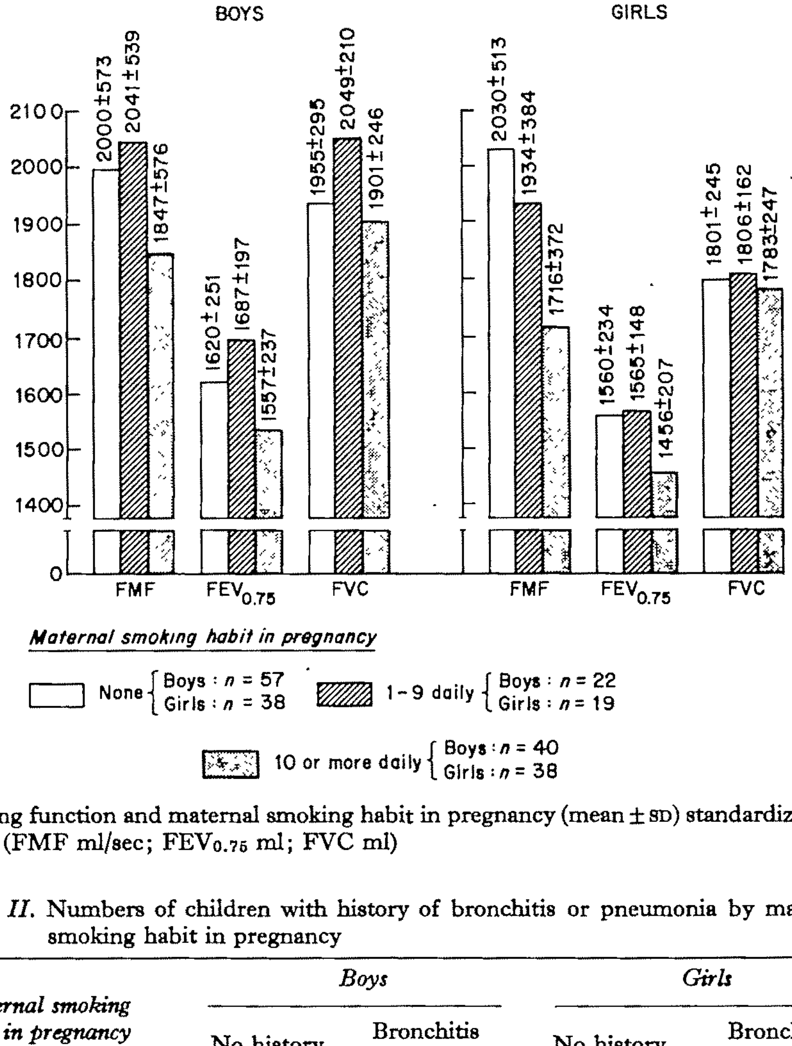

Fig. 2. Lung function and maternal smoking habit in pregnancy (mean ± SD) standardized to height of 130 cm (FMF ml/sec; FEV$_{0.75}$ ml; FVC ml)

Table II. Numbers of children with history of bronchitis or pneumonia by maternal smoking habit in pregnancy

Maternal smoking habit in pregnancy	*Boys*		*Girls*	
	No history	Bronchitis or pneumonia	No history	Bronchitis or pneumonia
None	49	8	34	4
1–9 daily	18	4	15	4
10 or more daily*	31	9	36	2
Total	98	21	85	10

* Very few mothers reported having smoked 20 or more cigarettes daily throughout pregnancy

with the offspring of mothers who had not smoked during pregnancy; the FVC is reduced to a lesser extent. The average reduction in FMF in male offspring of mothers who smoked 10 cigarettes or more daily is 8%; and in female offspring is 15%; the corresponding reductions in FEV$_{0.75}$ are 4% for males and 7% for females.

In Fig. 3 the relationship between the mother's current smoking habit and the lung

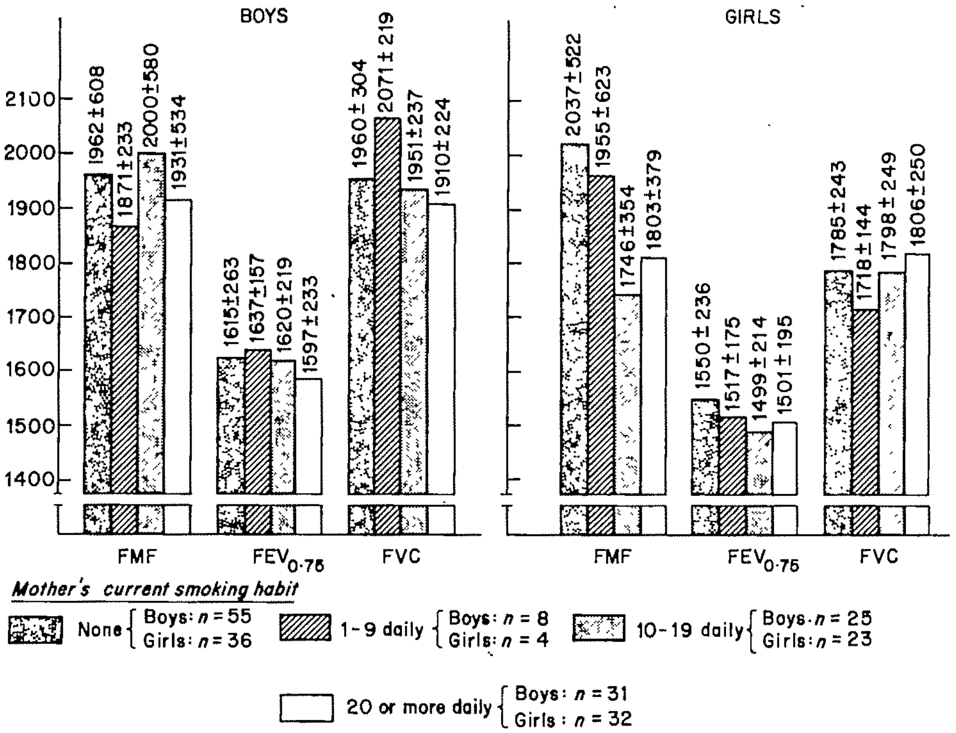

Fig. 3. Lung function and mother's current smoking habit (mean ± SD) standardized to height of 130 cm (FMF ml/sec; $FEV_{0.75}$ ml; FVC ml)

function of their children is examined; no consistent trends are shown although a reduction in FMF and $FEV_{0.75}$ in the female offspring of mothers who currently smoke 20 or more cigarettes daily is apparent.

Table III shows the children's lung function in relation to the mother's smoking habit during pregnancy and the current household smoking habit (this includes an estimate of the number of cigarettes currently smoked within the home by other household members —usually the father—in addition to the mother's own consumption). This analysis fails to show any further reduction in the lung function of children with increasing household cigarette consumption.

DISCUSSION

The present findings support the evidence for a relationship between early childhood bronchitis or pneumonia and subsequent impairment of lung function in children. Five of the mothers whose children had had bronchitis or pneumonia also said that their child had had asthma at some stage during the child's life. Since the majority of these children had lung function values which were close to the average values for each height group this subgroup of children did not contribute significantly to the trends shown in Fig. 1.

In the present study the impairment of lung function of children whose mothers smoked more than 10 cigarettes throughout pregnancy did not appear to be wholly

Table III. Lung function indices (mean, standardized to height of 130 cm) by maternal smoking habit during pregnancy and current household smoking habit (number of subjects shown in parentheses)

Lung function test	*Household smoking habit*	*Boys*			*Girls*		
		Maternal smoking in pregnancy			*Maternal smoking in pregnancy*		
		None	1–9 daily	10 or more daily	None	1–9 daily	10 or more daily
FMF (ml/sec)	None	1988 (18)			2088 (9)	2409 (1)	
	1–9 daily	1996 (15)	2095 (3)	1934 (2)	1770 (12)	2348 (2)	1346 (1)
	10–19 daily	1951 (17)	2102 (8)	1778 (12)	2264 (12)	1819 (9)	1702 (12)
	20 or more daily	2160 (7)	1983 (11)	1873 (26)	1969 (5)	1894 (7)	1739 (25)
$FEV_{0.75}$ (ml)	None	1557 (18)			1587 (9)	1776 (1)	
	1–9 daily	1682 (15)	1843 (3)	1754 (2)	1472 (12)	1608 (2)	1445 (1)
	10–19 daily	1593 (17)	1637 (8)	1521 (12)	1606 (12)	1521 (9)	1435 (12)
	20 or more daily	1727 (7)	1678 (11)	1557 (26)	1622 (5)	1575 (7)	1466 (25)
FVC (ml)	None	1879 (18)			1781 (9)	2038 (1)	
	1–9 daily	2036 (15)	2344 (3)	2197 (2)	1751 (12)	1712 (2)	1946 (1)
	10–19 daily	1928 (17)	1923 (8)	1901 (12)	1817 (12)	1791 (9)	1734 (12)
	20 or more daily	2027 (7)	2058 (11)	1875 (26)	1916 (5)	1818 (7)	1791 (25)

caused by an increased tendency to develop bronchitis or pneumonia in early childhood. A slightly greater proportion of boys whose mothers had smoked during pregnancy had a history of bronchitis or pneumonia compared to boys of mothers who had not smoked (Fig. 2), but this tendency is not apparent in girls.

A previous study by Colley et al. (1974) suggested that passive smoking by infants from parental cigarette consumption contributed towards the development of bronchitis or pneumonia in the first year of life. In the present study data on parental smoking habit during each child's first year of life are not available; current paternal smoking habit (recorded in total household smoking habit), however, which is unlikely to have altered substantially throughout the life of the child, does not contribute towards impairment of lung function in a child.

Respiratory morbidity in children varies with the social class of their families (Colley & Reid 1970). Fathers of children in the present study population were predominantly employed in manual and unskilled occupations; the social class of mothers who had smoked and those who had not smoked during pregnancy was therefore similar.

In a previous report on these data we showed that children's lung function differed in three areas of different housing (Yarnell & St Leger 1977). The relative impairment in lung function of children of mothers who smoked 10 or more cigarettes daily during pregnancy reported here is independent of the formerly reported association, however; this tendency is present in all areas of housing in girls and in all areas but one in boys.

In view of the known limitations of certain historical data (Hamman et al. 1975; Lunn et al. 1970), the present findings must be interpreted with some caution. They do suggest, however, that heavy smoking during pregnancy may have a direct effect on the offspring's subsequent lung function which persists at least into late childhood. As noted by Bland et al. (1974) mild impairment of lung function may not be of immediate clinical significance to individual children but may nevertheless indicate a predisposition to chronic bronchitis in adult life. This latent disposition would only be activated by additional factors in adult life; the most important of these is cigarette smoking.

Many studies have reported the long-term effects on the child of maternal smoking during pregnancy (reviewed by Rush & Kass 1972; Butler et al. 1972) but there are few reports of acute effects during pregnancy. Three such reports (Manning et al. 1975; Gennser et al. 1975; Manning & Feyerabend 1976) note that fetal breathing movements are inhibited by maternal cigarette smoking. If the findings of the present study are confirmed these reports may explain at least part of the impairment of lung function in children of mothers who smoked heavily during pregnancy of a mechanism which operates *in utero*.

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Tabulated details of the results of this study may be obtained directly from the authors.

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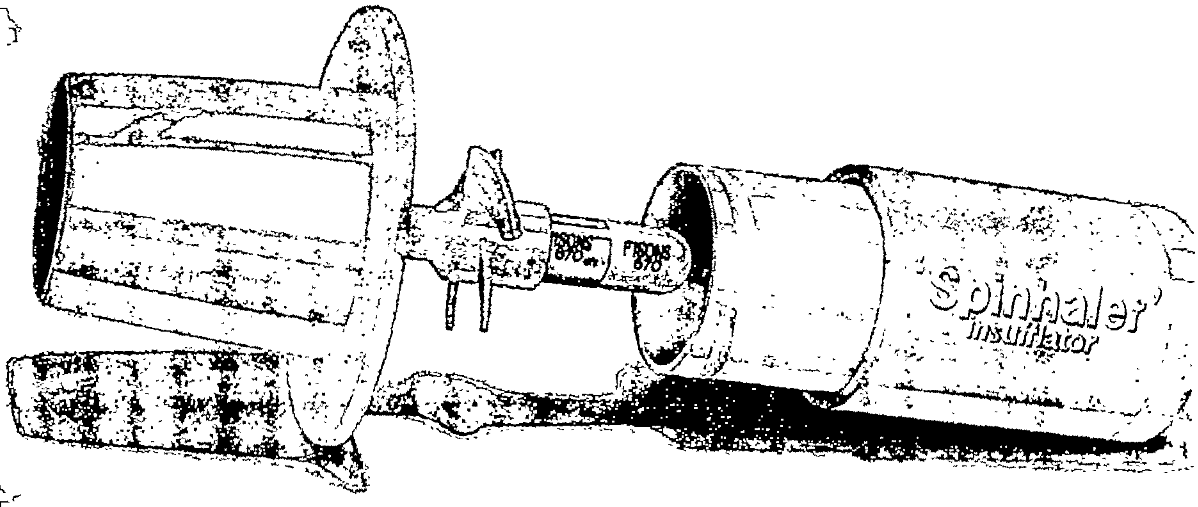

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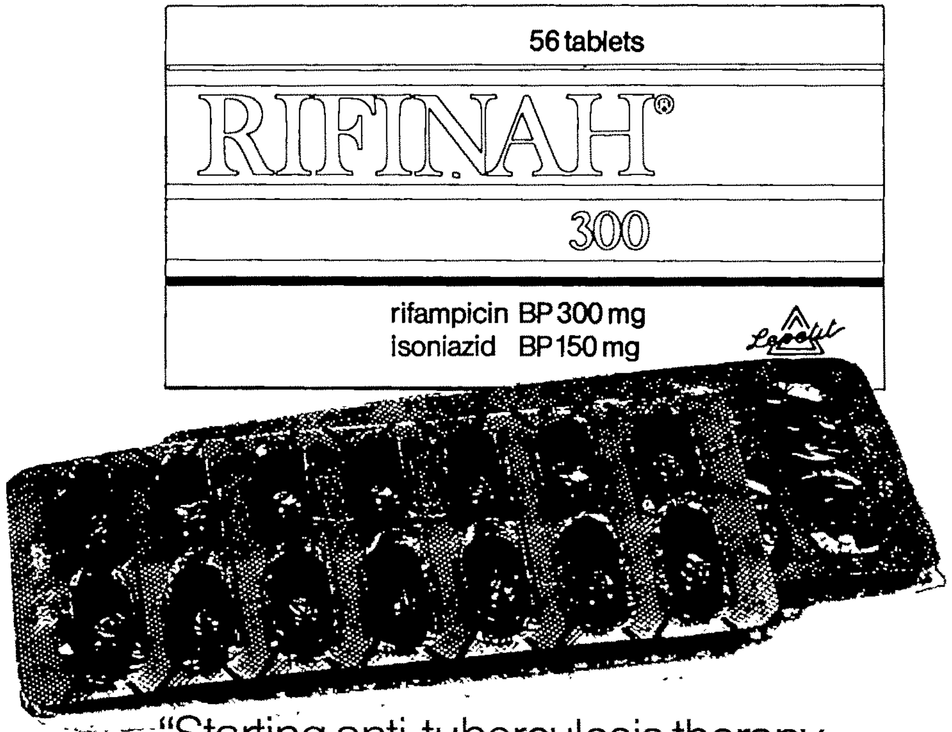

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INTERPRETATION OF BLOOD GAS ANALYSIS BY PHYSICIANS IN A COMMUNITY TEACHING HOSPITAL

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Summary

Forty-two interns and residents on the staff of a community teaching hospital were questioned to assess their understanding of blood gas abnormalities. Misunderstandings were such that 24% of the residents and interns might have given inadequate care had their interpretations dictated practice. Few therapeutic misadventures in fact occurred, largely because of supervision. Even without supervision, it is unlikely that much harm would have come about, partly because pattern recognition and rules of thumb provided adequate guidance and partly because no notice was taken of the results of the blood gas analysis anyway. Those who wish to promote rational practice should direct their educational efforts to improved understanding of the mechanisms of hypoxaemia and of the chemical, physiological and pathophysiological interactions of $P\text{CO}_2$, bicarbonate and pH in the various acid–base disorders.

INTRODUCTION

An important factor governing the cost and benefit of a laboratory investigation is the ability of the doctor ordering the test to interpret the results. This ability should normally be acquired during residency training and be based on an understanding of the underlying physiology acquired in medical school.

Blood gases are now measured in vast numbers, with a corresponding demand for instruction in their use. In this study we have attempted to assess the understanding of residents of the use of blood gases in training in order to identify those matters about which there is uncertainty, confusion or ignorance. This information should guide us as teachers and we hope may also lessen the cost of care by reducing the number of unnecessary measurements.

Methods

The survey was carried out in St Joseph's Hospital, Hamilton, Ontario, a 650-bed community and teaching hospital having 25 000 admissions per year. Blood gas analysis is provided by the Regional Respiratory Laboratory, which was established in 1968 as part of the Hamilton Regional Respiratory Programme. Two three-week periods were chosen for the survey, straddling a rotation of house staff so as to increase the number of physicians ordering blood gas analyses.

During the survey, 97 patients had gas analyses performed for the first time. The subjects of the study were the residents and interns ordering those 'first blood gas analyses'. Each subject was interviewed to gain information about his understanding of the physiology underlying blood gas analysis results and of the particular diagnostic and therapeutic use of the blood gas analysis he had ordered. We chose to question subjects about only 'first blood gas analyses' on the basis of a pilot survey which showed that a doctor's recall for any blood gas analysis other than the first in a series was poor and that the yield of new information from successive interviews was slight.

The subjects were interviewed by one of three senior residents in the respiratory programme (J.L.C.M., A.C.P.P. and S.O.P.), using a questionnaire drawn up with the help of three senior members of the department (E.J.M.C., N. L. Jones and M. T. Newhouse) and evaluated in a pilot study. Subjects were questioned as soon as possible after they had ordered the blood gas analysis; 70% were questioned within 24 hours, the remainder within 72 hours. Some subjects ordered several 'first blood gas analyses' and were interviewed several times, sometimes on the same day. This resulted in an improvement in subjects' scores and so we have included only the results of the first interview in this report to avoid the learning bias.

The questionnaire was designed to probe the subject's understanding of the physiology underlying blood gas disturbance and how this understanding related to the assessment and management of his patient. The questions (Appendix I) related to the patient; e.g. 'Suspecting this clinical diagnosis, what do you consider to be the physiological mechanisms causing the low $P\text{O}_2$ in this patient?' The answer would be probed to establish the understanding of factors influencing arterial $P\text{O}_2$ in general. In exploring the answers, we sought to avoid wrong classification of responses because of either unfamiliarity with physiological terms or familiarity with the terms without understanding. An answer such as 'V/Q' would not be accepted as appropriate or inappropriate until it was established whether 'V/Q' was an ill-understood catch phrase or a well-understood concept. Questions relating to the subject's physiological understanding of blood gas abnormalities were grouped into three categories: normal range, expected value and physiological mechanism.

Using the information gained about the patient and the subject's general understanding of blood gas analysis, we estimated the possible impact of the physiological understanding on that patient's care; for reasons given below the possible impact was not necessarily what happened in practice. We made a judgement of each physician's understanding of blood gas analysis, as related to the care of his patient, in three categories: diagnostic use, physiological interpretation and therapeutic implication. Diagnostic use refers to the pattern of blood gas values expected in a particular clinical situation; physiological interpretation as to how such change occurred; and therapeutic implications as to how such abnormalities might be reversed. The rating in each category depended on the least well understood blood gas variable relevant to the patient; for example, if the subject did not understand the therapeutic implications of a raised bicarbonate in a patient with chronic lung disease, he was rated accordingly, even though he showed good understanding of the other variables. A rating of 'good' was given when the physician showed reasonably complete understanding for all variables; 'adequate' when the level of understanding was such that no major mistakes were likely to be made, but where there were deficiencies in understanding; and 'inadequate' when there was a lack of understanding likely to cause an error in diagnosis or treatment.

RESULTS

During the survey, 270 blood gas analyses were performed by the Respiratory Laboratory. This number included 97 which were the first to be requested on a particular patient: there were 42 residents and interns (the subjects), responsible for ordering those 'first blood gas analyses' (Table I). The diagnoses which prompted the ordering of the blood gas analysis were mainly respiratory, cardiovascular or metabolic (Table II). Analysis of the subjects' understanding of the physiology underlying blood gas results showed that understanding of the mechanisms altering arterial blood $P\text{O}_2$ and bicarbonate was poor; a smaller number of physicians gave appropriate answers to these questions (Table III). Only 18% of the subjects knew how to calculate the alveolar–arterial oxygen tension gradient; when the calculated value was given to them, only 55% knew whether that value lay within the normal range.

The blood gas abnormalities that the subject expected to find in his patient were sufficiently erroneous to lead to possible misdiagnosis in 14% of cases (Table IV). This

Table I. Survey characteristics

Total number of blood gas analyses performed during the survey		270
Number of 'first blood gas analyses' performed during the survey		97
Resident staff responsible for ordering the 'first blood gas analysis'		42
Interns	15	
Residents	27	

Table II. Category of diagnosis prompting blood gas analyses

Category of diagnosis	%
Respiratory	42
Cardiovascular	22
Renal	5
Metabolic	19
Trauma	2
Surgical	6
Neurological	4

Table III. Physiological understanding of blood gas abnormalities

	Subjects (%) giving appropriate answers about			
	P_{O_2}	P_{CO_2}	pH	HCO_3
Normal range	93	90	100	88
Expected value	88	95	95	83
Physiological mechanism	81	90	88	81

Table IV. Predicted impact on care of patients

	Predicted impact on patient care		
	Good	Adequate	Inadequate
Diagnostic use	48	38	14
Physiological interpretation	20	40	40
Therapeutic implication	31	45	24

figure, when contrasted with the 41% of subjects in whom physiological interpretation was judged inadequate, indicates that pattern recognition played a larger part in the interpretation of blood gas analysis results than an understanding of the processes involved. In spite of the 24% possibility of therapeutic error (Table IV), in the 16 patients for whom therapeutic decisions were taken as a direct result of the blood gas analysis, only two therapeutic decisions were considered incorrect. In one case, uncontrolled oxygen therapy was given to a patient with known chronic pulmonary disease and whose blood gas analysis showed a raised bicarbonate. The other therapy considered incorrect was the administration of bicarbonate to correct acidaemia in a patient with respiratory failure. In all those cases in which therapy was not changed or started the decisions were considered to be correct. Thus, the observed therapeutic error of less than 10% is in contrast to the predicted possible error of 24%. As discussed later, this may have been due in part either to the fact that the blood gas findings were ignored or to the fact that therapy was decided by others.

Discussion

We surveyed 42 residents and interns (the subjects) who ordered blood gas analysis with the intention of establishing the understanding of the physiological and clinical meaning of the blood gas abnormalities and to estimate the possible results of such understanding on patient care. The study revealed several gaps in their understanding of blood gas and acid–base physiology. In spite of these gaps, clinical care was rarely compromised.

This study has two major sources of bias which must be questioned. First, are the subjects representative of those residents and interns who should understand blood gases? Second, were we fair in our judgements? Neither question is susceptible to a categorical answer, but we do not believe the biases invalidate our conclusions.

First, the subjects were not a casual sample or otherwise arbitrarily selected, they became subjects because in their training they ordered a blood gas determination on a patient for whom they were responsible. There is, however, reason to believe that the ordering of blood gases was more circumspect during the study, because 25% fewer blood gases were ordered during the survey than during a similar period immediately prior to the survey. Such circumspection probably arose because of the necessity to question each subject while the clinical circumstance in which he ordered and used the blood gas analysis was fresh in his mind. This meant that most residents and interns in the hospital were aware of the study. Thus the degree of physiological misunderstanding reported here is likely to be an underestimate since, knowing that he might be subject to the survey, the less comfortable a resident or intern felt about blood gas analysis, the less likely would he be to order one. This bias would give greater significance to our findings (Tables III, IV) which showed deficiencies in understanding sufficient to lead to inappropriate and possibly dangerous therapy by 24% of our subjects.

Second, our judgements could be challenged as being too demanding, but we believe they were fair because of the care taken in the design and application of the questionnaire and its modification in light of the pilot study. In some parts of the questionnaire used to reach these conclusions, the appropriateness of the response would not be disputed; in those areas where judgements had to be made, we believe that the decisions reached were fair because of the care taken to explore the subject's understanding. Any uncertainties arising during the survey were discussed with other members of the survey team. Such uncertainties were few, probably because of the experience in the pilot study and the care taken in the design and application of the questionnaire and interview. Comparison of the results in Table IV, which involved the most judgement, showed that the three residents conducting the interviews scored similar percentages in each category. Overall, we do not regard our judgements as too harsh: in classifying responses as good, adequate and inadequate, the criterion was the implication for patient care rather than an academic grading of understanding. On the basis of our experience as examiners and candidates, we are confident that the understanding we expected was no greater than that for a pass in a qualifying examination in internal medicine and somewhat below the pass standard in a second- or third-year examination in physiology in medical school.

Despite these deficiencies in understanding, few therapeutic errors were made. This fortunate state of affairs was, of course, largely due to the fact that as residents the subjects were being supervised. However, it also seemed from the answers to the questionnaire that it resulted from observation of certain rules without concern about the reason why: e.g 'don't give chronic bronchitics uncontrolled oxygen'.

It is a generally held belief that the use of investigations in medicine should be based on an understanding of basic mechanisms. On the face of it, our study questions that belief, in that despite considerable ignorance there was little danger. Two possible explanations are obvious: first, interpretation of blood gases does not require understanding; second, blood gases are done as a work-up without any particular use in mind. We suspect the second is the more likely. The value of this survey to those who believe in rational practice based on scientific understanding is in delineating the areas of deficiency so that education may be directed towards them (Table III). With regard to $P\text{O}_2$, the relationship between inspired $P\text{O}_2$ and alveolar $P\text{O}_2$ was poorly understood: less than one in five of the residents and interns knew how to calculate the alveolar–arterial oxygen tension gradient and barely half of them knew whether the value when calculated lay within the normal range. This meant neglect of 'shunt' or 'venous admixture' both as qualitative concepts and quantitative assessments of the gas exchanging status of the lung. With regard to arterial blood $P\text{CO}_2$, a raised $P\text{CO}_2$ was often attributed entirely to gas exchange abnormalities in the lung, without appreciation that abnormal ventilation/blood flow relationships alone do not cause a rise in $P\text{CO}_2$ unless there is also a gross impairment of ventilatory ability, or an abnormality of ventilatory control, or a combination of both. The poor understanding of the factors affecting bicarbonate concentration is of concern, as a major use of blood gas analysis is in the evaluation of acid–base status (Table II). This poor understanding largely stems from the oversimplified physiological interpretation of chemical values. For example, a normal or only slightly elevated bicarbonate concentration in the presence of a high $P\text{CO}_2$ might be taken to signify an acute 'uncompensated' respiratory acidosis without the possibility of coexistent metabolic acidosis being recognized. To understand fully these possibilities in acid–base assessment the physician needs to be aware of the magnitude of expected changes in complicated respiratory disturbances, both acute and chronic.

We found that only 16 of 97 patients had therapy changes as a direct result of the blood gas analysis. This might suggest excessive use of blood gas analysis and would support Griner (1972) who, studying pulmonary oedema, drew attention to lack of evidence of benefit from greater use of blood gas measurement and emphasized the expense resulting from such use. Our study was not designed to evaluate whether arterial blood gases were being used excessively, but on reviewing our data we were surprised to find that a sound case could be made for ordering 82% of the blood gas analyses. We would attribute this high figure to the particular circumstances of our study and consider it untypical of blood gas analysis usage in general.

It might be considered that the level of understanding and use shown by the physicians surveyed with regard to blood gas analysis is better than expected when compared to other laboratory tests. Albeit that the clinical judgement taken was generally satisfactory, the demonstrated deficiencies in understanding do not allow for complacency when they relate to a test used in acute and rapidly changing situations in which misinterpretation of results can be dangerous. It is hoped that this survey will encourage educational efforts directed to improving the understanding of the physiology underlying blood gas abnormalities.

APPENDIX I

Survey Questions

1. What was the clinical diagnosis at the time of ordering the blood gas analysis?
2. (*a*) Why did you order the blood gas analysis?
   (*b*) For which blood gas values ($P\text{O}_2$, $P\text{CO}_2$, pH, HCO_3)?
3. What blood gas abnormalities did you expect to find?
   (*a*) $P\text{O}_2$—high, normal, low, very low (<30)
   (*b*) $P\text{CO}_2$—very high (>80), high, normal, low
   (*c*) HCO_3—high, normal, low
   (*d*) pH—acid, normal, alkaline
4. Considering the clinical diagnosis, what do you consider to be the physiological mechanism causing the abnormality in:
   (*a*) $P\text{O}_2$
   (*b*) $P\text{CO}_2$
   (*c*) HCO_3
   (*d*) pH
5. What therapy(ies) did you start (change) to correct the observed (expected) blood gas abnormalities?
6. (*a*) Which blood gas abnormality prompted each therapy?
   (*b*) How do you consider the therapy would correct the abnormality?
7. With regard to the blood gas results on your patient, is the $P\text{O}_2$ ($P\text{CO}_2$, HCO_3, pH, H^+) in the normal range?
8. (*a*) What is the alveolar–arterial oxygen tension difference?
   (*b*) Is this value normal?

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Short Review

HLA PHENOTYPES IN ASBESTOS WORKERS

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Large-scale epidemiological studies have demonstrated the close association between the intensity of exposure to asbestos dust (i.e. dose) and the prevalence of asbestosis. However, amongst those exposed to the largest amounts of dust for the longest periods of time, only a proportion of workers develop lung disease. Moreover there appears to be no close relation between the severity of radiographic abnormalities and the estimated dose of inhaled asbestos. These facts suggest that factors other than dose and duration of exposure also influence the development of asbestosis in individual workers. Several studies have been undertaken in attempts to identify possible host factors associated with an increased susceptibility to the damaging effects of asbestos dust.

Certain histocompatibility antigens (HLA phenotypes) have been associated with various diseases, the strongest being HLA-B27 in ankylosing spondylitis (Brewerton et al. 1973). It was therefore of considerable interest that Merchant et al. (1975) reported results from a pilot survey indicating an increased prevalence of HLA-B27 in asbestos workers compared to a normal population; these results were confirmed by Matej and Lange (1976).

Three more detailed controlled studies have now been reported in which an attempt has been made to compare HLA phenotypes in asbestos workers developing asbestosis compared with those without evidence of lung disease but of comparable age and asbestosis exposure (Evans et al. 1977; Huuskonen et al. 1979; Gregor et al. 1979). No statistical difference in the prevalence of B27 was found between subjects with asbestosis and case controls in any of these reports. A trend towards a higher prevalence was found by Gregor et al. (1979), but the opposite was found by Huuskonen et al. (1979). Conversely Evans et al. (1977) suggested that B5 was found more frequently amongst those not developing asbestosis and might therefore relate to some protective factor. This suggestion is supported indirectly by Gregor et al. (1979) who found that this phenotype was more frequent amongst those with apparently stable disease compared with a group with progressive asbestosis when observed over three years. A suggestion that B18 might also have a protective role (Huuskonen et al. 1979) was not supported in either of the two other control studies.

Very recently a further study has been completed in which the HLA phenotypes in 64 asbestos workers without radiographic abnormality were compared with 166 workers with various radiographic changes (Darke et al. 1978). This report differed from that reported by Gregor et al. (1979), in that it was not designed as a case control study. No significant differences were observed in the frequency of any individual phenotype when corrected for the number of analyses undertaken. B27, however, was found twice as frequently amongst those with evidence of pulmonary fibrosis (asbestosis) compared with control asbestos workers. The study reported by Darke et al. (1978) did not, however, confirm the observation by Merchant et al. (1975), confirmed by Gregor et al. (1979), that B27-positive workers with asbestosis had a shorter length of exposure to asbestos than asbestotic subjects without this phenotype. The divergent results might be due at least in part to the different types of exposure. The population studied by Darke et al. (1979) was dockyard workers only and that of the other two groups of workers a mixed population including laggers, factory and dockyard workers.

The relatively minor inconsistencies in the data from these three studies may in part be due to relatively small numbers; 27 pairs were studied by Evans et al. (1977) and 37 pairs by Huuskonen et al. (1979). There is also a substantial difference in the prevalence of various HLA phenotypes in the control populations used in the various studies. This may well be due to population or racial differences. Whatever the explanation, it emphasizes the difficulties of comparing different studies and of obtaining consistent and meaningful results. HLA population studies are inherently difficult because of the large numbers of comparisons which have to be undertaken and for which statistical allowance has to be made.

The overall conclusion from these three recent controlled studies would seem to be that there is no important and consistent difference in the frequency of HLA phenotypes on the A, B or C loci in subjects with asbestosis compared with case controls. Thus such studies cannot be used to identify individuals particularly susceptible or resistant to the tissue damaging effects of asbestos dust.

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When the bronchodilator alone is inadequate, what next?

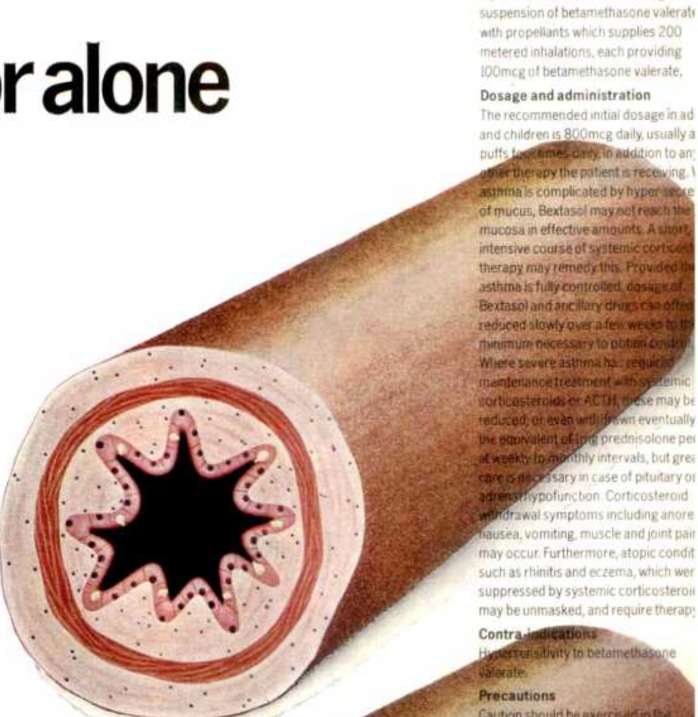
In controlling chronic asthma, the bronchodilator is usually the first line of attack. Often it will be the only treatment required.

In many cases, however, bronchodilators need to be given continuously and even then a number of patients will not be controlled satisfactorily—probably because the asthma is complicated by inflammation which bronchodilators will not control.

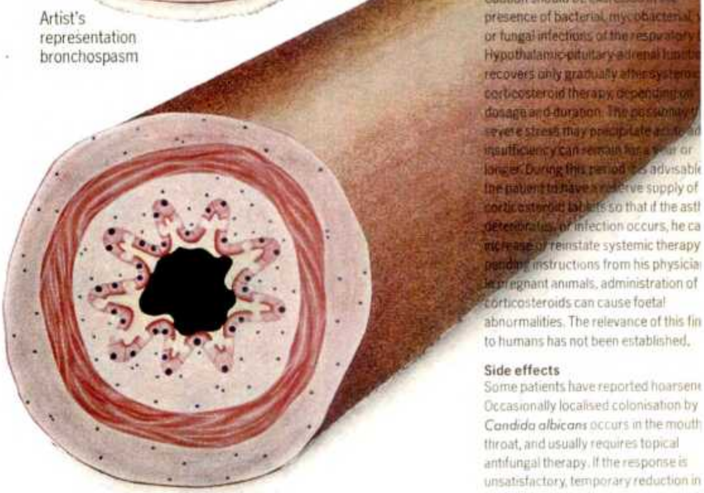
So when a second line of attack is required, Bextasol effectively controls the inflammatory process within the lungs and provides ideal prophylaxis of both intrinsic and extrinsic asthma. It offers steroid control without systemic side effects and usually produces a significant improvement in lung function.

In addition, no adverse effects on lung tissue have been reported after five years' clinical experience of inhaled steroid therapy.

In short, Bextasol inhaler allows the asthmatic to breathe and to live life to the full.



Artist's representation bronchospasm



Bronchospasm complicated by mucosal oedema and hypersecretion of mucus.

the clear decision

BEXTASOL
Bextasol
Bextasol Inhaler
It is dangerous to exceed the recommended dose
Glaxo

(betamethasone valerate)

Prescribing information

Presentation

A pressurised aerosol containing a suspension of betamethasone valerat with propellants which supplies 200 metered inhalations, each providing 100mcg of betamethasone valerate.

Dosage and administration

The recommended initial dosage in ad and children is 800mcg daily, usually a puffs four times daily, in addition to an other therapy the patient is receiving. asthma is complicated by hypersecre of mucus, Bextasol may not reach the mucosa in effective amounts. A short, intensive course of systemic corticost therapy may remedy this. Provided th asthma is fully controlled, dosage of Bextasol and ancillary drugs can ofte reduced slowly over a few weeks to th minimum necessary to obtain contro Where severe asthma has required maintenance treatment with systemic corticosteroids or ACTH, these may be reduced, or even withdrawn eventually the equivalent of 1mg prednisolone pe at weekly to monthly intervals, but gre care is necessary in case of pituitary o adrenal hypofunction. Corticosteroid withdrawal symptoms including anore nausea, vomiting, muscle and joint pai may occur. Furthermore, atopic condit such as rhinitis and eczema, which we suppressed by systemic corticostero may be unmasked, and require therap

Contra-indications

Hypersensitivity to betamethasone valerate.

Precautions

Caution should be exercised in the presence of bacterial, mycobacterial, or fungal infections of the respiratory Hypothalamic-pituitary-adrenal functio recovers only gradually after systemic corticosteroid therapy, depending on dosage and duration. The possibility t severe stress may precipitate acute ad insufficiency can remain for a year or longer. During this period it is advisabl the patient to have a reserve supply of corticosteroid tablets so that if the ast deteriorates, or infection occurs, he ca increase or reinstate systemic therapy pending instructions from his physicia In pregnant animals, administration of corticosteroids can cause foetal abnormalities. The relevance of this fin to humans has not been established.

Side effects

Some patients have reported hoarsen Occasionally localised colonisation by *Candida albicans* occurs in the mouth throat, and usually requires topical antifungal therapy. If the response is unsatisfactory, temporary reduction in dosage of Bextasol often speeds resol

See Data Sheet for complete informat

Product Licence number: 4/0142

Basic NHS cost (exclusive of VAT): £ per inhaler.

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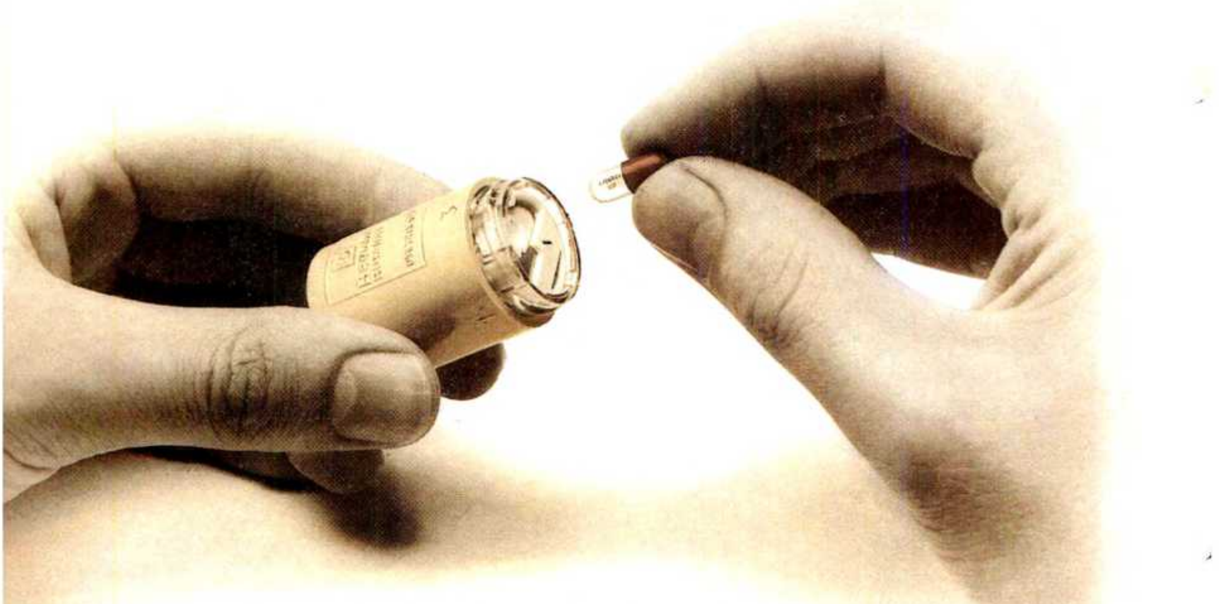
An important development in th

NEW

BECOTIDE

(Beclomethasone dipropionate BP inhalation cartridges)

Improved control for a wider ra



or use in conjunction with the Becotide Rotahaler as a
reath-actuated alternative to Becotide Inhaler

A GREATER DEGREE OF CERTAINTY –

ECOTIDE ROTACAPS PRESCRIBING INFORMATION

ESENTATION

cotide Rotacaps, an alternative inhalation form of beclomethasone dipropionate to
cotide Inhaler, are especially valuable for treating patients who are unable to use
essurised inhalers effectively or who might use them incorrectly.
cotide Rotacaps contain a mixture of microfine beclomethasone dipropionate BP
d larger particle lactose in buff or chocolate-brown/colourless hard gelatine
rtridges. Each Becotide Rotacap contains 100 micrograms (buff) or 200 micrograms
ocolate-brown) of beclomethasone dipropionate BP and is marked Becotide 100
Becotide 200. The contents of a Rotacap are inhaled using a specially developed
vice called a Rotahaler which cuts the cartridge into two halves that rotate and
ease the drug when the patient inhales. This breath actuation is very sensitive and
the drug is fully available even at the lowest inspiratory rates.

DICATIONS

cotide Rotacaps are indicated for a wide range of patients with bronchial asthma.
ese patients include: those whose asthma is becoming worse and the relief
vided by bronchodilators is less effective; those who are inadequately controlled
sodium cromoglycate in addition to bronchodilators; those with severe asthma
o are dependent on systemic corticosteroids, or adrenocorticotrophic hormone
TH) or its synthetic equivalent.
cotide Rotacaps are particularly important for managing severe asthma in children

DOSAGE AND ADMINISTRATION

Becotide Rotacaps are for inhalation use only, using a Becotide Rotahaler. For optimum results Becotide Rotacaps should be used regularly.

Adults: One 200 micrograms Rotacap, three or four times a day is the usual maintenance dose.

Children: One 100 micrograms Rotacap two, three or four times a day, according to the response.

CONTRA-INDICATIONS

No specific contra-indications to Becotide Rotacaps are known, but special care is necessary in patients with active or quiescent pulmonary tuberculosis.

PRECAUTIONS

Patients should be instructed in the proper use of the Rotahaler to ensure that the drug reaches the target areas within the lungs. They should also be made aware that Becotide Rotacaps have to be used regularly for optimum benefit.

The maximum daily intake of beclomethasone dipropionate should not exceed 1mg; significant reduction of plasma cortisol levels has been reported in patients who received twice this amount.

Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

If there is no response to therapy within a week in patients previously not treated with systemic steroids or ACTH then consideration should be given to the probability that excessive mucus in the bronchi has prevented the drug from penetrating to its site of

nhaled steroid therapy of asthm

ROTACAPS*

e of patients with chronic asthma

Becotide Inhaler is well established for the treatment of chronic asthma where inflammatory changes within the lungs reduce the response to bronchodilators; and for many previously steroid-dependent patients in eliminating or greatly reducing their need for systemic steroids, particularly severely asthmatic children who would be at risk from systemic side effects such as stunting of growth.

However, there are patients who do not obtain maximum effectiveness from Becotide Inhaler, and the Rotacaps/Rotahaler System has been developed with them in mind providing –

Breath-actuated control – for children, and those elderly or arthritic patients who may find it easier and more reliable.

Avoidance of faulty inhaler technique – for those patients who cannot co-ordinate the action of breathing in with the activation of a pressurised aerosol.

A better guarantee of effectiveness – for patients in whom Becotide Inhaler has not provided the anticipated benefit probably because of inadequate delivery of drug.

Appropriate routine prophylaxis – a way of helping to ensure that Becotide is used routinely by those patients who might misunderstand its role.

BETTER GUARANTEE OF EFFECTIVENESS

apparent ineffectiveness before the trial of a short course of systemic steroid in relatively high dosage has been given to control secretion of mucus and other inflammatory changes in the lungs.
When transferring patients to Becotide Rotacaps from systemic steroids, please refer to the detailed procedure described in the Data Sheet.

SIDE EFFECTS
No major side effects attributable to the use of recommended doses of Becotide Rotacaps have been reported. Candidiasis of the mouth and throat (thrush) occurs in some patients; patients with high blood levels of Candida precipitins, indicating a previous infection, are more likely to develop this complication. The condition usually responds to topical antifungal therapy without discontinuing treatment with Becotide Rotacaps.

PACKAGE QUANTITIES
Becotide Rotacaps 100 micrograms in containers of 100 – (PL 0045/0119)
Becotide Rotacaps 200 micrograms in containers of 100 – (PL 0045/0120)

Further information is available on request.

WELLCOME MUSEUM OF THE HISTORY OF MEDICINE

In 1976 the Wellcome Museum of the History of Medicine was transferred on permanent loan to the Science Museum to form the basis of a national medical collection. Dr Brian Bracegirdle was appointed Keeper of the Collection which formed a new department at the Science Museum. To display the collection two large galleries will be opened at South Kensington. The Upper Wellcome Gallery, which is scheduled to open early in 1981, is to be arranged as a chronological history of medicine from the earliest times to the present day.

As the Historian to the Wellcome Museum of the History of Medicine at the Science Museum I should like to make an appeal to your readers for certain historical medical artefacts. I have two roles in the display and development of the collection. First, I have to exhibit a display dealing with the history of medicine since 1900. This is an area in which the collection is relatively deficient. Second, I am endeavouring to establish an archive of important contemporary medical technology. Subsidiary to this I am drawing up a central catalogue of the whereabouts of important objects, only acquiring them if their owners were seeking a good home.

Since the Wellcome Galleries will contain a section on the history of respiratory medicine I am very anxious to acquire artefacts relating to this discipline. This is particularly so in the case of material dating from the last 50 or 60 years, for its historical value is usually unrecognized and it is often just thrown away as it is replaced by newer technology. For example, I am seeking such objects as artificial pneumothorax apparatus, for instance of the Lillingston, Homes–Wingfield and Parry–Morgan varieties, also early spirometers, bronchoscopes, and aspirators such as Burrell's, Martin's or Gauvian's. I am also seeking carbon dioxide indicators such as Frederica's, Haldane apparatus, peak-flowmeters and de Bono whistles. In short I am trying to build up a significant collection of objects allied to your specialty. We can offer here excellent curation and storage of such artefacts, many of which will go on display. We undertake, of course, to provide the transport and all costs involved. We also have a small purchase fund in the case of objects of special importance.

Perhaps then I could ask you to let me know of the existence of such items, however unimportant they might at first appear. I should also like to hear of the whereabouts of established collections so that I might record their existence. The whole project, it seems to me, is of immense importance, for its outcome will be the preservation for the nation of a permanent record of 20th century medical technology.

Please contact Dr Christopher Lawrence, MB, ChB, MSc, Historian, Wellcome
Museum of the History of Medicine, Science Museum, South Kensington,
London SW7 2DD
Tel. 01-589 3456 ext 565 Telex 21200

Br. J. Dis. Chest (1979) *73*, 245

THE ROLE OF HISTOCOMPATIBILITY (HLA) ANTIGENS IN ASBESTOSIS

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Summary

Histocompatibility antigens on the A, B and C loci have been studied in 172 asbestos workers, 92 of whom had radiographic evidence of asbestosis and 80 of whom had normal radiographs. Within each population, 77 were selected who matched for age, sex, duration from first exposure, duration of exposure and approximate heaviness of exposure. Results were also compared with 174 normal unexposed volunteers.

No differences of statistical significance were found in the frequency of histocompatibility antigens tested when the matched or the total population of asbestos workers with and without asbestosis were compared. There was, however, a consistent trend of increase in B27 amongst those with asbestosis (11%) and this reached conventional significance ($P < 0.05$) when the 92 asbestotics were compared with the whole group having normal radiographs (asbestos workers 5.0% and volunteers 5.2%). Amongst the group having asbestosis, those with HLA-B27 had a significantly shorter exposure to the dust (13.5 years) compared with those without asbestosis (22.3 years), although the mean radiographic profusion score for the two categories was similar.

No statistical differences could be found when B5, B8 and B12 were analysed in a similar way, but there was a trend suggesting that B5 was less frequent amongst a small group of cases showing radiographic progression over a three-year follow-up, compatible with the suggestion that this antigen might be linked with with some protective effect.

INTRODUCTION

The development of pulmonary fibrosis as a consequence of inhalation of asbestos dust has been known since the sixteenth century (Agricola 1556). In studies where the amount of dust in the environment has been monitored with reasonable accuracy it has been observed that not all individuals develop the same degree of fibrosis for the same exposure (Fournier-Massey et al. 1971; Becklake et al. 1972). Thus a possible biological difference in the host has to be considered.

As a part of a larger project attempting to define host factors we have studied the HLA phenotypes in patients with asbestosis and in subjects with an approximately similar exposure, but with a normal chest radiograph.

The interest in histocompatibility antigens in disease in recent years led to identification of various disease associations, the strongest being HLA-B27 and ankylosing spondylitis (Brewerton et al. 1973). Merchant et al. (1975) reported that HLA-B27 occurred more frequently among 56 asbestos workers (18%) who had been referred to the

Pneumoconiosis Medical Panel because of suspected asbestosis than amongst a control population (5%). A similar result was reported by Matej and Lange (1976): they found HLA-B27 in 27% of 22 patients with asbestosis compared with 10% amongst 112 exposed workers from the same asbestos textile factory who did not have clinical evidence of pulmonary fibrosis. The preliminary report of Merchant et al. (1975) also suggested that workers possessing HLA-B27 and having radiographic evidence of disease tended to have a shorter dust exposure than those without this antigen. This additional evidence tends to support the suggestion that B27 might perhaps relate to enhanced susceptibility to the tissue-damaging effects of asbestos dust.

More recently Evans et al. (1976) tested 37 patients with asbestosis and compared them with 37 control subjects matched for equivalent asbestos exposure, all working in the same textile factory. No significant differences in HLA frequencies were detected in this small group. These authors showed that B12 might be associated with a greater degree of pulmonary fibrosis and that B5 might have a protective role since it was found less frequently amongst the group with asbestosis.

In the present study we report the frequency of B27 in a group of patients with radiographic evidence of asbestosis compared with that in asbestos workers having an approximately similar exposure, but with normal chest radiograph. We have also compared the frequency of certain clinical and occupational factors in groups of asbestos workers with and without certain selected histocompatibility antigens which have been implicated either in asbestosis or in some types of immunological disorders.

Methods

The subjects studied

Since 1967, 250 individuals with a history of asbestos exposure referred to the Pneumoconiosis Medical Panel (PMP, London) for assessment have been seen at the Brompton Hospital, where a clinical questionnaire is completed, chest radiographs taken and routine lung function tests performed. Only some of these subjects have abnormal radiographs. An attempt was made to recall all 116 of those having a radiograph profusion score (ILO-UC Classification 1971) of 1/1 or greater, as agreed between the authors. Of these 16 had died and six had moved and could not be traced. Two subjects refused to reattend. A total of 92 asbestos workers ('index cases') with an agreed radiographic pulmonary abnormality were typed for histocompatibility antigens.

A total of 80 asbestos workers with a normal chest radiograph ('controls') were identified either from the PMP or from the East Ham Chest Clinic where ex-workers from an asbestos factory have been followed up.

From these two populations 77 index cases were matched for sex and (to within five years) duration of and duration from first exposure to asbestos ('matched index cases') with 77 'control' cases ('matched controls'). As far as possible the two groups were also matched for approximate severity of exposure as judged by their job history within the industry (Harries 1971).

In this study 31 index cases and 25 controls (20 'matched index' and 21 'matched controls') were included in our earlier study (Merchant et al. 1975). Thus a total of 61 new index and 55 new controls have been studied.

The populations of asbestos workers have been compared also with a random non-exposed group of 174 apparently healthy volunteers drawn from the same region in south-east England.

HLA typing

The HLA typing was done by a two-stage microcytotoxicity testing (Kismeyer-Nielsen & Kjerbye 1967) using 2000 lymphocytes per test. The volume of antibody was 1 μl and rabbit complement 5 μl. Incubations were at room temperature for 30 minutes in the first stage and for one hour after the addition of complement. Living and dead cells were scored by Trypan blue exclusion. The antisera used conformed to international standards laid down at the IVth Histocompatibility Workshop.

RESULTS

The frequency of HLA types in the 92 'index' cases and the 80 asbestos 'controls' is set out in Table I. The data for the 'matched index' and 'matched controls' is set out in Table II. The increased frequency of B27 in the group of index cases is confirmed, but the difference between index and exposed control groups does not reach statistical significance when either the total population of asbestos workers or the matched cases alone are considered. The frequency of B27 in the 80 exposed controls and in 174 volunteers was very similar, 5.0% and 5.2% respectively: this combined control group shows a frequency of B27 significantly less than the index group ($P < 0.05$ using χ^2 with Yates correction). Bonferroni correction is not applicable when testing for B27 in this

Table I. Frequency of histocompatibility antigens in asbestos workers

HLA type	*Index cases with abnormal X-rays ($n = 92$)*	*Control cases with normal X-rays ($n = 80$)*	*Control ($n = 80$) and unexposed ($n = 174$) cases*
A locus			
1	34 (37.0%)	28 (35.0%)	90 (35.4%)
2	48 (52.2%)	38 (47.5%)	118 (46.5%)
3	20 (21.7%)	24 (30.0%)	74 (29.1%)
9	10 (10.9%)	10 (12.5%)	40 (15.7%)
10	9 (9.8%)	8 (10.0%)	32 (12.6%)
11	15 (16.3%)	11 (13.8%)	34 (13.4%)
28	7 (7.6%)	8 (10.0%)	19 (7.5%)
19	24 (26.1%)	20 (25.0%)	55 (21.7%)
blank	15 (16.3%)	13 (16.3%)	46 (18.1%)
B locus			
5	11 (12.0%)	11 (13.8%)	34 (13.4%)
7	17 (18.5%)	22 (27.5%)	78 (30.7%)
8	31 (33.7%)	20 (25.0%)	65 (25.6%)
12	26 (28.3%)	20 (25.0%)	68 (26.8%)
13	3 (3.3%)	6 (7.5%)	20 (7.9%)
w35	11 (11.8%)	7 (8.8%)	31 (12.2%)
w40	9 (9.8%)	12 (15.0%)	26 (10.2%)
14	8 (8.7%)	8 (10.0%)	17 (6.7%)
w15	11 (12.0%)	10 (12.5%)	24 (9.4%)
w16	4 (4.4%)	5 (6.3%)	13 (5.2%)
w17	9 (9.8%)	7 (8.8%)	27 (10.6%)
18	9 (9.8%)	7 (8.8%)	24 (9.4%)
w21	7 (7.6%)	3 (3.8%)	9 (3.5%)
w22	4 (4.4%)	4 (5.0%)	10 (3.9%)
27	11 (12.0%)	4 (5.0%)	13 (5.1%)*
Ty-W 37	3 (3.3%)	2 (2.5%)	3 (1.2%)
blank	9 (9.8%)	11 (13.8%)	41 (16.1%)

* The frequency of B27 was less in the combined control groups than in the index cases ($P < 0.05$, χ^2 using Yates correction).

Table II. Frequency of histocompatibility antigens in asbestosis*

	Matched index cases	*Matched control cases*
A locus		
1	30 (39.0%)	28 (36.4%)
2	42 (54.6%)	37 (48.1%)
3	17 (22.1%)	24 (31.2%)
9	8 (10.4%)	9 (11.7%)
10	8 (10.4%)	6 (7.8%)
11	14 (18.2%)	12 (15.6%)
28	5 (6.5%)	8 (10.4%)
19	19 (24.7%)	17 (22.1%)
blank	9 (11.7%)	13 (16.9%)
B locus		
5	16 (13.0%)	11 (14.3%)
7	16 (20.8%)	21 (27.3%)
8	27 (35.1%)	21 (27.3%)
12	24 (31.2%)	18 (23.4%)
13	3 (3.9%)	6 (7.8%)
40	8 (10.4%)	11 (14.3%)
14	5 (6.5%)	9 (11.7%)
15	9 (11.7%)	7 (9.1%)
16	3 (3.9%)	4 (5.2%)
17	6 (7.8%)	7 (9.1%)
18	6 (7.8%)	3 (3.9%)
w22	4 (5.2%)	4 (5.2%)
27†	9 (11.7%)	4 (5.2%)
Ty-W 37	8 (3.9%)	1 (1.3%)
blank	7 (9.1%)	11 (14.3%)

* Results were not significant, χ^2 with Yates correction.

† $0.1 < P < 0.2$ (matched proportions).

study because the present investigation has been preceded by a pilot survey suggesting an increased frequency of this antigen.

Amongst the index cases having comparable radiographic abnormalities as judged by the mean profusion score of irregular opacities, the duration of exposure to asbestos dust was significantly shorter (mean 13.5 years) in the B27 positive cases compared to those not possessing this antigen (mean 22.6 years) ($P < 0.02$, Student's *t*-test) (Table III).

Table III. Duration of asbestos exposure to diagnosis of asbestosis in B27-positive and B27-negative subjects

	B27-positive ($n = 11$)	*B27-negative* ($n = 81$)
X-ray score	Mode 2/2 Range 1/2 to 2/3	Mode 2/2 Range 1/2 to 3/3
Duration of exposure (years, Mean ± SD)	13.5±9.45	22.6±11.8
Duration from first exposure (years, Mean ± SD)	26.4±12.8	25.1±11.8

$P < 0.02$ (Student's *t*-test).

Table IV. Comparison of occupational and clinical features of 172 asbestos workers with certain histocompatibility antigens

	B5		*B8*		*B12*		*B27*	
	+ve	−ve	+ve	−ve	+ve	−ve	+ve	−ve
No. in group	22	150	51	121	46	126	15	157
Age (years, Mean ± SD)	53.8 ± 12.4	55.2 ± 8.6	56.3 ± 6.9	55.1 ± 8.6	52.6 ± 10.5	55.1 ± 8.6	58.7 ± 8.5	55.2 ± 8.6
Duration of exposure (years, Mean ± SD)	20.4 ± 9.6	20.2 ± 11.2	17.7 ± 8.8	20.3 ± 11.2	21.5 ± 11.4	19.8 ± 11.1	16.9 ± 12.8	20.3 ± 11.2
Time from first exposure (years, Mean ± SD)	25.7 ± 12.4	27.8 ± 11.6	25.7 ± 11.3	27.9 ± 11.6	27.1 ± 11.1	27.6 ± 11.7	26.4 ± 12.7	27.9 ± 11.6
Heavily exposed workers (%)	53.8	71.4	78.4	71.2	80.0	72.1	69.2	72.0
Chronic bronchitis (MRC criteria) (%)	24.9	38.8	37.0	39.6	44.0	38.9	53.3*	38.1*
History of arthritis (%)	14.3	22.2	26.8	21.8	14.3	22.1	33.3	22.4
Severity of dyspnoea:								
Grades 2, 3 and 4 (%)	35.7	39.5	51.2	40.2	28.5	39.2	38.5	39.1
Severe pleural disease:								
Grade 2 (%)	30.8	23.2	30.7	23.5	18.8	22.9	15.4	23.3
ANA +ve (%)	30.8	20.5	14.6	20.8	26.5	21.1	38.5	20.6
DAT +ve (%)	15.4	16.5	24.3	16.0	17.6	15.4	15.4	16.7

* Statistically significant difference, $P < 0.05$.

The distribution of other HLA types in index and control groups was comparable and the small differences noted are not statistically significant when either the total populations or the matched groups are compared.

Antigens B27, B12, B8 and B5 have been subject to further analysis. The factors compared included age, sex, past or present history of arthritis, smoking, chronic bronchitis using MRC criteria (1965), asbestos exposure characteristics, degree of dyspnoea, radiographic severity of asbestosis, pleural disease and the presence of autoantibodies. The results in the total asbestos exposed population are shown in Table IV. This table shows that the clinical features studied are very similar when asbestos workers with and without B5, B8, B12 and B27 are considered. The only feature to reach a conventional level of statistical significance is a greater frequency of chronic bronchitis amongst those having B27 compared to those without this antigen. The table also shows that the observation that the B27 positive workers had a significantly shorter length of exposure compared with those without this antigen, cannot be accounted for by the inclusion of a greater number of heavily exposed individuals in the B27 positive group.

Table V. Certain histocompatibility antigens in 57 asbestos workers followed over minimum of three years

HLA	*Progression on paired film analysis*	*No progression with at least 3 years follow-up*
B5	1/17 (5.3%)	5/40 (12.5%)
B8	5/17 (29.4%)	10/40 (25.0%)
B12	4/17 (23.5%)	12/40 (30.0%)
B27	3/17 (17.6%)	5/40 (12.5%)

In our population of 172 asbestos workers 57 were followed up over a period of at least three years. Seventeen of these 57 workers showed radiographic evidence of progression of asbestosis as judged by paired film analysis, while the 40 subjects remaining showed no progression with at least a three-year observation period. The frequency of B5, B8, B12 and B27 antigens in the different groups is shown in Table V. Amongst these small numbers the frequency distribution of workers possessing these antigens does not reach statistical significance when progressing and non-progressing cases are compared.

DISCUSSION

The present study shows a trend towards an increased frequency of HLA-B27 amongst asbestos workers with radiographic evidence of asbestosis when compared with a large number of unaffected asbestos workers and normal controls. On the basis of these data the relative risk of those with B27 antigen developing asbestosis is 2.4 times that of the controls. This finding is consistent with the earlier report of Merchant et al. (1975) and that of Matej and Lange (1976). The finding is consistent with the hypothesis that the presence of this factor may be associated with an increased susceptibility to the damaging effects of asbestos on the lung. The hypothesis is supported also by the finding that amongst the population with radiographic asbestosis, those with HLA-B27 had a significantly shorter duration of exposure compared to those without this antigen despite the fact that the radiographic profusion score was similar in the two groups. This finding confirms the earlier report by Merchant et al. (1975). The association between HLA-B27 and asbestosis, however, is far too weak for screening for this HLA type to be useful for detection of susceptible individuals.

Clearly, these conclusions are only valid if the exposure to asbestos dust was similar in the B27 positive and negative workers. While we have no evidence to the contrary, and indeed the proportion of the B27 positive workers judged as heavily exposed on assessment of their jobs was less than that of the B27-negative cases, no information is available on fibre counts. In this group of workers, each was involved in a wide range of different jobs over very many years and many were laggers undertaking work in all sorts of uncontrolled environments; others were dock workers and shipwrights.

Several studies of HLA antigens in asbestos workers are now being reported from various countries. In some the number of index cases is quite small and the frequency of different HLA types in the control populations shows considerable variation. These two factors probably account for the rather different results reported. A common feature, however, is that the differences from control populations are relatively minor.

Large numbers of cases have to be studied over longer periods of time for meaningful results to be obtained regarding factors predisposing to progression. In this relatively small series, no significant association between HLA and progression could be identified. The lesser frequency of B5 amongst the progressing cases, however, is consistent with the suggestion made by Evans et al. (1976) that this antigen might exert a protective role. In our main series, however, the frequency of B5 was similar amongst workers with and without asbestos (12% and 13.5% respectively).

We conclude that the frequency differences of HLA antigens in exposed workers who do and do not develop asbestosis are very slight and do not provide a clinically useful indicator of enhanced susceptibility. Further studies might more profitably be directed to the study of other fundamental questions such as those relating to individual fibrogenetic responses to tissue damaging agents.

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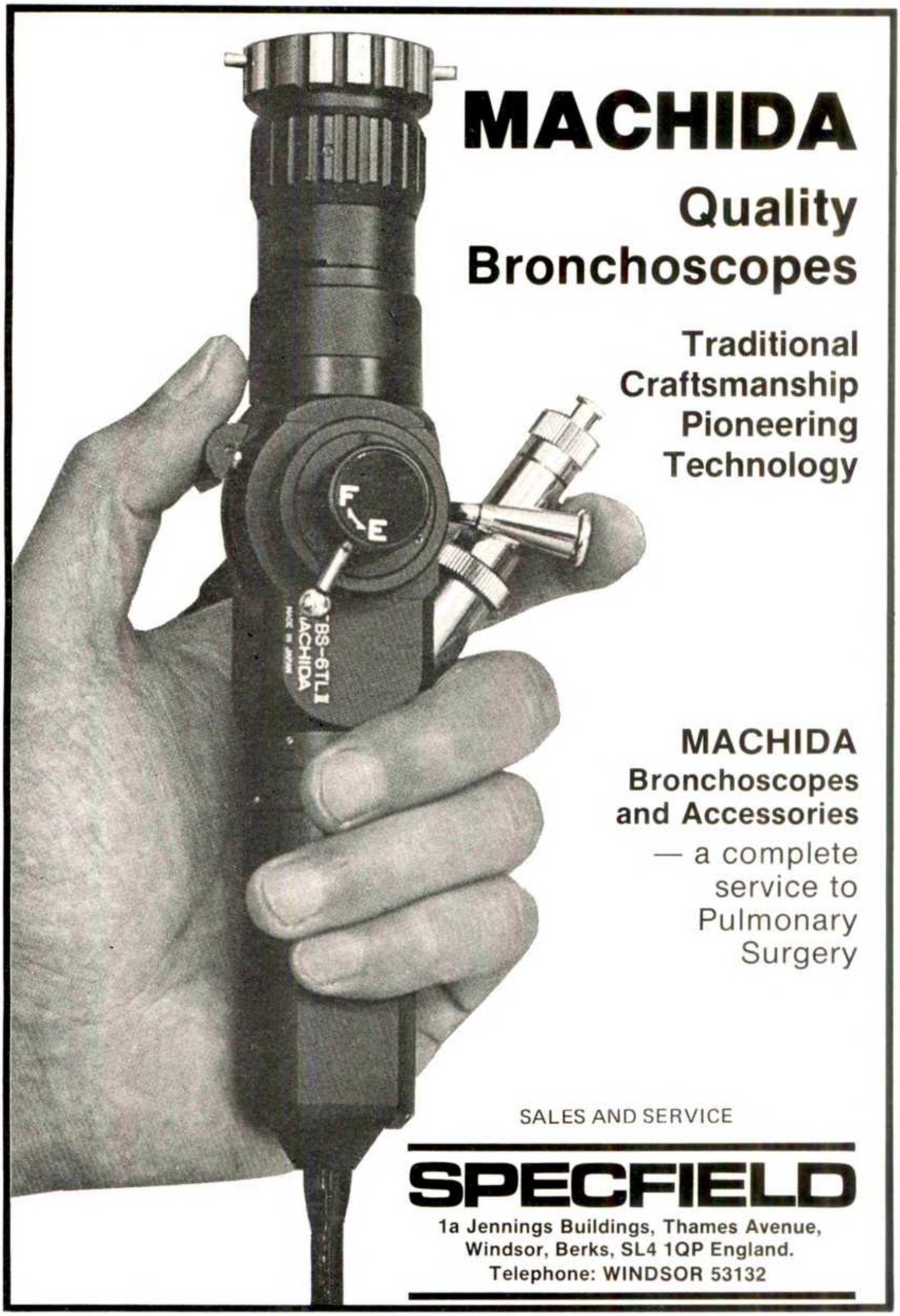

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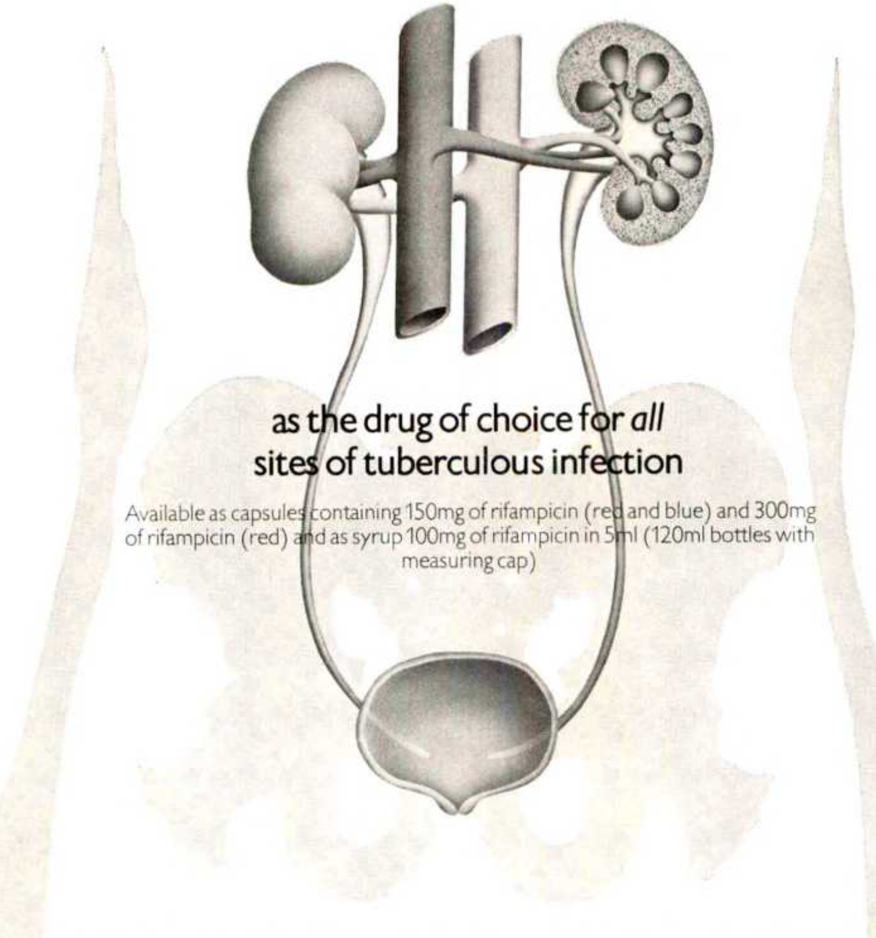

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HLA-B18 ANTIGENS AND PROTECTION FROM PULMONARY FIBROSIS IN ASBESTOS WORKERS

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Summary

HLA antigens were identified in 64 patients with radiographic asbestosis and 37 matched controls with equivalent asbestos exposure but no radiographic pulmonary fibrosis. A high prevalence of HLA-B18, B27 and Cw2 was found in the controls. This result might indicate that the possessors of these HLA antigens are thus protected from the development of diffuse pulmonary fibrosis from asbestos exposure. Signs of susceptibility were not demonstrated.

The radiographic severity and progression of asbestosis were not associated with any of the HLA antigens tested.

Introduction

Merchant et al. (1975) suggested that presence of the HLA antigen B27 might indicate an increased susceptibility to the damaging effects of asbestos dust on the lungs. Matej and Lange (1976) reported that 27% of 22 asbestos workers with asbestosis had HLA-B27 in comparison to 9.8% of 112 control workers without asbestosis. Evans et al. (1977) determined HLA antigens in 37 patients with asbestosis and 37 matched controls with equivalent asbestos exposure but no radiographic pulmonary fibrosis. They found no significant differences in the prevalence of HLA antigens in the two groups and in the controls who had not been exposed to asbestos.

This paper reports the prevalence of HLA antigens in a series of Finnish asbestos workers with and without radiographic pulmonary fibrosis and in blood donors who had not been exposed to asbestos dust.

Patients and Methods

Of patients in whom asbestosis had been diagnosed in the Institute of Occupational Health in Helsinki, 64 were re-examined for this study. A matched control with equivalent asbestos exposure but no radiographic pulmonary fibrosis was found for 37 patients (Table I). We recorded the occupation, sex, age, year of entry and age at entry into jobs exposed to asbestos dust and smoking habits. We also made a clinical examination, including lung function tests and chest radiographs, of all asbestosis subjects. The matched reference group was submitted to a clinical examination including chest radiographs. The subjects had worked in the insulation industry (as insulators and as asbestos sprayers), in the asbestos cement product factory and in other industries including, for example, ship-building. Their relevant occupational history is summarized in Table I.

In this study the diagnostic criteria of asbestosis were as follows:

1. History of occupational exposure to asbestos dust.
2. Positive radiographic features according to the ILO-UC 1971 classification of pneumoconiosis (1971).

Table I. Occupational, clinical, physiological and radiological data on the exposed referents and asbestosis subjects

	Exposed referents (*n*=37)	*Asbestos subjects with matched referents* (*n*=37)	*All asbestosis patients* (*n*=64)
Sex (M:F)	32:5	32:5	53:11
Age (years)			
<40	4	8	4
40–9	15	15	11
50–9	14	11	22
>60	4	3	27
Mean and range	49.5 (33–60)	53.2 (30–70)	56.7 (30–77)
Year entered			
<1940	—	1	11
1940–9	7	16	23
1950–9	14	13	21
>1960	16	7	9
Range	1940–70	1937–66	1926–66
Age entered			
<20	3	7	9
20–9	17	14	25
30–9	12	12	23
>40	5	4	7
Mean and range	30.1 (17–52)	28.1 (15–49)	28.8 (15–49)
Years exposed			
<10	2	4	7
10–19	20	14	20
20–9	13	15	22
>30	2	4	15
Mean and range	17.0 (4–36)	19.3 (6–34)	21.3 (3–44)
Smokers	27	32	46
Clubbing	—	16	27
Crepitations	1	20	41
VC (% predicted)	ND	80.5±18.5	75.2±19.2
FEV_1 (% predicted)	ND	82.0±19.4	75.7±20.1
TF (% predicted)	ND	94.3±22.5	87.2±23.5
Radiographic profusion category*			
0	5	20	27
1	—	14	25
2	—	3	12

ND=Not determined.

* 0=0/1, 1/0 and 1/1; 1=1/2, 2/1 and 2/2; 2=2/3 or more.

Additional supporting features included dyspnoea on effort, persistent basal crepitations, clubbing of the fingers and reduction in vital capacity, FVC$_1$ and the single-breath carbon monoxide transfer factor, but these were not used as obligatory diagnostic criteria.

Thirty-three HLA antigens were determined by the two-stage lymphocytotoxicity test (Amos et al. 1969) from the freshly separated peripheral lymphocytes of 64 patients with asbestosis and from the relevant 37 matched control subjects. The antigen frequencies of these groups were compared with those of 900 Finnish blood donors.

The statistical analyses were made with the χ^2 test and, in some comparisons when frequencies were small, with Fisher's exact probability test.

Table II. Prevalence of HLA antigens in the various groups studied

HLA antigen	*Exposed referents* ($n=37$)	*Asbestosis subjects with matched referents*	*All asbestosis subjects* ($n=64$)	*Blood donors* ($n=900$)
A locus				
1	4 (10.8%)	6 (16.2%)	10 (15.6%)	20.1%
2	21 (56.8%)	26 (70.3%)	39 (60.9%)	54.0%
3	15 (40.5%)	19 (51.4%)	29 (45.3%)	44.4%
9	8 (21.6%)	5 (13.5%)	14 (21.9%)	16.2%
10	3 (8.1%)	0	1 (1.6%)	7.8%
11	2 (5.4%)	2 (5.4%)	4 (6.3%)	8.8%
28	6 (16.2%)	6 (16.2%)	10 (15.6%)	11.3%
w19	8 (21.6%)	5 (13.5%)	9 (14.1%)	19.6%
B locus				
5	2 (5.4%)	5 (13.5%)	8 (12.5%)	11.9%
7	12 (32.4%)	10 (27.0%)	24 (37.5%)	24.3%
8	4 (10.8%)	6 (16.2%)	11 (17.2%)	20.0%
12	3 (8.1%)	4 (10.8%)	12 (18.8%)	15.4%
13	1 (2.7%)	2 (5.4%)	3 (4.7%)	6.0%
14	0	0	0	0.3%
15	6 (16.2%)	8 (21.6%)	16 (25.0%)	20.1%
17	0	0	0	4.3%
18	7 (18.9%)	0	3 (4.7%)	10.0%
27	11 (29.7%)	6 (16.2%)	9 (14.1%)	14.0%
37	0	1 (2.7%)	1 (1.6%)	1.6%
40	9 (24.3%)	8 (21.6%)	11 (17.2%)	17.9%
w16	4 (10.8%)	4 (10.8%)	5 (7.8%)	9.3%
w21	0	0	0	0.4%
w22	0	3 (8.1%)	4 (6.3%)	5.0%
w35	10 (27.0%)	13 (35.1%)	16 (25.0%)	27.0%
w4	17 (45.9%)	16 (43.2%)	28 (43.8%)	52.1%*
w6	36 (97.3%)	33 (89.2%)	57 (89.1%)	88.6%*
C locus				
w1	6 (16.2%)	9 (21.6%)	11 (17.2%)	14.3%†
w2	9 (24.3%)	3 (8.1%)	3 (4.7%)	7.7%‡
w3	8 (21.6%)	13 (35.1%)	23 (35.9%)	32.1%†
w4	8 (21.6%)	8 (21.6%)	13 (20.3%)	19.2%§
w5	0	1 (2.7%)	1 (1.6%)	
w6	1 (2.7%)	2 (5.4%)	2 (3.1%)	7.4%‖
blank	12 (32.4%)	10 (27.0%)	22 (34.4%)	34.1%¶

* Determined in 501 blood donors. § Determined in 338 blood donors.
† Determined in 483 blood donors. ‖ Determined in 462 blood donors.
‡ Determined in 418 blood donors. ¶ Determined in 384 blood donors.

RESULTS

Differences were not found for any of the variables when subjects with and without matched referents were compared. Thus both categories could be treated as one group.

The results of the clinical, physiological and radiological findings of the different asbestos-exposed groups are summarized in Table I.

Table II presents the prevalence of HLA antigens in the two matched groups with and without asbestosis, in all asbestosis subjects, and in the 900 blood donors. The prevalence of HLA-B18 was decreased in the asbestosis subjects in a comparison with the exposed referents or the blood donors. The prevalences of HLA-B27 and Cw2 were increased in the 37 exposed control subjects. Table III shows the statistical comparison for HLA-B18, B27 and Cw2 in the various groups.

Table III. Comparison of the prevalence of HLA-B18, B27 and Cw2 in the various groups studied

Groups compared[*]	*HLA-B18*	*HLA-B27*	*HLA-Cw2*
1 *v* 2	$\chi^2=5.68$ $P<0.05$	$\chi^2=1.22$ $P>0.05$	$\chi^2=2.49$ $P>0.05$
1 *v* 3	$\chi^2=3.86$ $P<0.05$	$\chi^2=2.71$ $P>0.05$	$\chi^2=6.88$ $P<0.01$
1 *v* 4		(x) $P<0.05$	(x) $P<0.01$
2 *v* 4	(x) $P<0.05$		

[*] Group 1 = exposed referents ($n=37$); Group 2 = asbestosis subjects with matched referents ($n=37$); Group 3 = all asbestosis subjects ($n=64$); Group 4 = blood donors ($n=900$).

Statistical tests were made with the chi-square test and, when frequencies were small (x) with Fisher's exact probability test.

The clinical examination revealed six lung cancers among the asbestosis subjects. All of them were cigarette-smokers. In five of the six cases of lung cancer we determined HLA antigens. There were no significant differences in HLA antigens between this group and all workers with asbestosis or the blood donors (Table IV).

There was no association between any HLA antigen and the severity of asbestosis seen in the chest radiographs (Table V). Neither was there an association with the progression of diffuse fibrosis observed in the chest radiographs.

The speed of developing pulmonary fibrosis during exposure to asbestos was not associated with any particular HLA antigen (Table VI).

Table IV. HLA phenotypes of the asbestosis subjects with lung cancer

Case	*HLA phenotypes*
1	A2; B5, 7, w4, w6; C−
2	A1, 2; B15, 27, w4, w6; Cw1, 3
3	A3; Bw35, w6; Cw4
4	A2, w19; B12, 13; w4; w6
5	A2, 3; B8, 18, w6; C−

Table V. HLA antigens in radiographic categories*

HLA antigens	*Radiographic profusion category*		
	0 (*n*=27)	1 (*n*=25)	2 (*n*=12)
A locus			
1	5 (18.5%)	4 (16.0%)	1 (8.3%)
2	14 (51.9%)	19 (76.0%)	6 (50.0%)
3	15 (55.6%)	8 (32.0%)	6 (50.0%)
9	8 (29.6%)	3 (12.0%)	3 (25.0%)
10	0	0	1 (8.3%)
11	2 (7.4%)	1 (4.0%)	1 (8.3%)
28	5 (18.5%)	4 (16.0%)	1 (8.3%)
w19	1 (3.7%)	6 (22.2%)	2 (16.7%)
B locus			
5	3 (11.1%)	3 (12.0%)	2 (16.7%)
7	8 (29.6%)	10 (40.0%)	6 (50.0%)
8	5 (18.5%)	4 (16.0%)	2 (16.7%)
12	4 (14.8%)	4 (16.0%)	4 (33.3%)
13	1 (3.7%)	1 (4.0%)	1 (8.3%)
14	0	0	0
15	5 (18.5%)	7 (28.0%)	4 (33.3%)
17	0	0	0
18	1 (3.7%)	1 (4.0%)	1 (8.3%)
27	3 (11.1%)	4 (16.0%)	2 (16.7%)
37	1 (3.7%)	0	0
40	7 (25.9%)	3 (12.0%)	1 (8.3%)
w16	2 (7.4%)	3 (12.0%)	0
w21	0	0	0
w22	3 (11.1%)	1 (4.0%)	0
w35	10 (37.0%)	5 (20.0%)	1 (8.3%)
w4	11 (40.7%)	11 (44.0%)	6 (50.0%)
w6	23 (85.2%)	24 (96.0%)	10 (83.3%)
C locus			
w1	6 (22.2%)	4 (16.0%)	1 (8.3%)
w2	1 (3.7%)	2 (8.0%)	0
w3	7 (25.9%)	10 (40.0%)	6 (50.0%)
w4	7 (25.9%)	3 (12.0%)	3 (25.0%)
w5	0	1 (4.0%)	0
w6	1 (3.7%)		1 (8.3%)
blank	10 (37.0%)	9 (36.0%)	5 (25.0%)

* Profusion category 0=0/1, 1/0 and 1/1,
1=1/2, 2/1 and 2/2,
2=2/3 or more.

DISCUSSION

Similar exposure to asbestos dust does not have the same effect on all exposed subjects. Asbestosis, i.e. fibrotic reaction to the noxious agent, may be understood as a defence mechanism of the organism. If immunological defence is genetically controlled, fibrotic reactions may also be. Patients with asbestosis are known to express various forms of

Table VI. HLA antigens and the length of exposure of the subjects to asbestos dust

HLA antigen	*Exposure years* <20		*Exposure years 20 or more*	
	Exposed referents ($n=22$)	Subjects with asbestosis ($n=26$)	Exposed referents ($n=15$)	Subjects with asbestosis ($n=38$)
A locus				
1	1 (4.5%)	4 (15.6%)	3 (20.0%)	6 (15.8%)
2	12 (54.5%)	17 (65.4%)	9 (60.0%)	22 (57.9%)
3	7 (31.8%)	12 (46.2%)	8 (53.3%)	17 (44.7%)
9	5 (22.7%)	6 (23.1%)	3 (20.0%)	8 (21.1%)
10	1 (4.5%)	0	2 (13.3%)	1 (2.6%)
11	1 (4.5%)	0	1 (6.7%)	4 (10.5%)
28	6 (27.3%)	2 (7.7%)	0	8 (21.1%)
w19	6 (27.3%)	4 (15.4%)	2 (13.3%)	5 (13.2%)
B locus				
5	1 (4.5%)	2 (7.7%)	1 (6.7%)	6 (15.8%)
7	7 (31.8%)	7 (26.9%)	5 (33.3%)	17 (44.7%)
8	1 (4.5%)	6 (23.1%)	3 (20.0%)	5 (13.2%)
12	1 (4.5%)	6 (23.1%)	2 (13.3%)	6 (15.8%)
13	1 (4.5%)	1 (3.8%)	0	2 (5.3%)
14	0	0	0	0
15	3 (13.6%)	9 (34.6%)	3 (20.0%)	7 (18.4%)
17	0	0	0	0
18	4 (18.2%)	1 (3.8%)	3 (20.0%)	2 (5.3%)
27	7 (31.8%)	3 (11.5%)	4 (26.7%)	6 (15.8%)
37	0	0	0	1 (2.6%)
40	7 (31.8%)	3 (11.5%)	2 (13.3%)	8 (21.1%)
w16	3 (13.6%)	3 (11.5%)	1 (6.7%)	2 (5.3%)
w21	0	0	0	0
w22	0	2 (7.7%)	0	2 (5.3%)
w35	6 (27.3%)	6 (23.1%)	4 (26.7%)	10 (26.3%)
w4	8 (36.4%)	11 (42.3%)	9 (60.0%)	17 (44.7%)
w6	21 (95.5%)	23 (88.5%)	15 (100.0%)	34 (89.5%)
C locus				
w1	7 (31.8%)	3 (11.5%)	4 (26.7%)	8 (21.1%)
w2	6 (27.3%)	2 (7.7%)	3 (20.0%)	1 (2.6%)
w3	5 (22.7%)	11 (42.3%)	3 (20.0%)	12 (31.6%)
w4	3 (13.6%)	6 (23.1%)	5 (33.3%)	7 (18.4%)
w5	0	0	0	1 (2.6%)
w6	1 (4.5%)	1 (3.8%)	0	1 (2.6%)
blank	7 (31.8%)	8 (30.8%)	5 (33.3%)	14 (36.8%)

autoimmune reactions (Turner-Warwick 1977). Consequently, the correlation between asbestosis and the (immune response associated) HLA system may shed light on the role of inheritance in the aetiology of fibrosis. The few reports dealing with HLA antigens and asbestosis suggest some associations, however, with different associations in different reports. The true nature of associations remains to be explained.

Unlike Merchant et al. (1975) and Matej and Lange (1976) we found no increase of HLA-B27 in asbestosis patients. On the contrary, it was increased in those exposed but not diseased and might thus be an indicator of protection against the development of pulmonary diffuse fibrosis. HLA-Cw2 followed the same pattern, perhaps because B27 and Cw2 are frequently inherited together (in the same HLA haplotype). HLA-B18 seems to indicate protection from the disease even more clearly, since only very few individuals carrying this specificity had asbestosis. This finding is in agreement with the reports of Major et al. (1975), who stated that progressive massive fibrosis occurs infrequently in coal miners with B18. Evans et al. (1977) may well have been speaking of the same factor that is connected with B18, when they suggested a protective influence associated with Bw35, since these antigens belong to the same serologically cross-reacting group (i.e. possible descendants of the same primordial gene which is linked to the 'protector' gene?). Our study did not implicate any HLA specificity as a sign of susceptibility to asbestosis. Also the progression of the disease appeared to be independent of the HLA type of the patient.

Six of the asbestosis patients had lung cancer. This group was too small, however, to form a basis for conclusions concerning HLA associations. A follow-up of a larger series of lung cancer patients could possibly provide more information, because the carcinogens in asbestos dust and tobacco seem to collaborate. Asbestos workers who smoke have a 17 to 90 times greater chance of developing lung cancer than non-smoking non-asbestos workers (Selikoff et al. 1968; Meurman et al. 1974). Still, cancer does not develop in all subjects with increased risk—perhaps because of genetic resistance?

A combined study of HLA antigens and autoimmune phenomena in asbestos workers might help to answer the question whether there are resistance or susceptibility factors operating in the development of fibrosis.

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A TRIAL OF HOUSE DUST MITE EXTRACT IN BRONCHIAL ASTHMA

MITE ALLERGY SUBCOMMITTEE OF THE RESEARCH COMMITTEE OF THE
BRITISH THORACIC ASSOCIATION*

Summary

Patients with asthma considered to be due to house dust mite allergy were allocated at random to treatment with (*a*) increasing weekly injections of house dust mite extract for 18 weeks followed by monthly injections to complete 18 months of treatment; (*b*) similar injections for 18 weeks followed by placebo injections up to 18 months or (*c*) placebo injections for 18 months. Fifty-six patients completed at least six months of observation.

In patients *not* on corticosteroids the treated group did a little better than the controls, as judged by night asthma scores, discontinuation of bronchodilators and overall blind assessment of the records by a panel of independent physicians. No benefit was apparent by extending treatment from 18 weeks to 18 months. In contrast, patients on corticosteroids given placebo injections did a little better than the treated group.

The extract used was stronger than the commercially available preparation and the injections had to be stopped in one-sixth of the patients because of side-effects. The improvement in patients not on corticosteroids in this trial was of doubtful clinical importance.

INTRODUCTION

Some physicians believe that attempts at hyposensitization to house dust extract are worth while in asthmatics who become more wheezy when exposed to house dust. The British Tuberculosis Association trial in 1968, however, found no difference between a commercially available preparation and placebo injections.

By the time the results were published it had become recognized that the major allergen in house dust was the house dust mite, *Dermatophagoides pteronyssinus*. Aqueous extracts of the mite later became available for treatment and in 1972 the Research Committee of the British Thoracic Association resolved to carry out a further multicentre double blind controlled study in patients with asthma.

Materials and Methods

Patients

Physicians with an interest in asthma in the British Isles were asked to submit patients with asthma which they considered to be caused by house dust mite allergy. The patients had to have (*a*) a positive skin prick test with a 1.2% (w/v) solution of *D. pteronyssinus* extract, together with (*b*) a worsening of asthma after exposure to dust from house cleaning or bed making and/or a positive nasal provocation test with one of three strengths (0.005, 0.04 or 0.3%) of *D. pteronyssinus* extract. Eligible patients were aged 16 to 50 years, born in the British Isles of any racial group and with dyspnoea and wheezing at least once a week in the previous year and severe enough at times to interfere with normal activities.

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* Members of the Mite Allergy Subcommittee were: D. Davies (*Chairman*), G. Berry (*Statistician*), E. Hills, S. Lal (*Coordinator*), M. McAllen, J. Morrison Smith and J. Pepys.

Excluded were patients (*a*) likely to have seasonal exacerbations of asthma, (*b*) with symptoms due to animal danders when continued exposure was likely, (*c*) with other recognizable unavoidable triggers, except exercise, (*d*) previously given a course of dust or mite extract injections, and (*e*) who were pregnant.

The consent of the patient was obtained. In the initial weeks they were taught to keep a daily record card. This recorded the severity of day and night asthma, nasal symptoms and the use of bronchodilators, sodium cromoglycate and corticosteroid tablets and aerosols. Skin prick tests with nine other common allergens were done and the forced expiratory volume in one second (FEV_1) before and after the inhalation of a bronchodilator was recorded. All subjects were given advice about house dust suppression, the details being left to individual physicians.

Treatment

An aqueous extract of *D. pteronyssinus* which had been grown on animal tissue of non-dermal origin (Bencard) was put up in strengths of 0.005, 0.04 and 0.3%. The control solution contained the vehicle only (glycerated extraction medium).

Group A patients were given weekly injections of 0.1, 0.2, 0.3, 0.5, 0.7 and 1 ml, starting with the lowest concentration and increasing to higher ones. The schedule was modified to deal with local or generalized reactions. When the top dose had been reached (usually after 18 weeks) or, in a few cases, the maximum tolerated dose, this was continued at monthly intervals until 18 months' treatment had been completed.

Group B were given similar injections for 18 weeks but, when the maximum or maximum-tolerated dose was reached, placebo injections were given at monthly intervals to complete 18 months.

Group C were given placebo injections for 18 months.

Patients were allocated randomly to one of the three treatments separately within centres and according to whether or not they were receiving corticosteroids (orally or by inhalation).

When the patients had kept satisfactory records for four weeks, injections were started. They were seen by their physician at monthly intervals for two years. He issued new diary cards and recorded changes in severity of asthma and medicaments, absence from work and the FEV_1. Every six months he also repeated skin and nasal tests with *D. pteronyssinus* extract, assessed changes in asthma severity and checked whether dust suppression measures were still being carried out. Total IgE and IgE and IgG specific to *D. pteronyssinus* were measured before the start of treatment and every six months for a total of two years.

IgE specific to mite extract was measured by the radioallergosorbent test (RAST) (Ceska et al. 1972) and specific IgG by radio-immunoelectrophoresis, a modification of the method of Scheidegger (1955). All measurements were done in one batch at the end.

Assessment of progress

The serial records were used to assess the changes in every patient in two ways:

1. The mean values of the day and night asthma scores, use of bronchodilators, sodium cromoglycate and corticosteroids and FEV_1 expressed as a percentage of the predicted value were all calculated for the pre-treatment period (entry values and month 1). The same parameters were calculated again for months 2 and 3 and thereafter for each three month period up to 24 months. The changes in each variable from the pre-treatment value were calculated and the effects of treatment were assessed by analysis of variance on each variable separately and for each of the eight time periods from months 2–3 to months 21–24.

2. The six physicians on the subcommittee considered all the variables together in making a combined assessment of each patient's progress. For every patient they used the mean values of each variable grouped into the time periods used in the first method of assessment and also the

six-monthly assessments by the patient's own doctor. Two print-outs were prepared for every patient, one to cover the first six months, i.e. up to the end of the weekly injection schedule, and the other to cover all 24 months of the trial. The trial regimen was not included in the print-outs which were distributed in random order to all six physicians on the subcommittee. Each physician independently made an assessment of every patient's progress using five categories: much better, better, no change, worse and much worse. In making the assessments the physicians used their judgement to eliminate the effects of change in bronchodilator, sodium cromoglycate or corticosteroid treatment. For example, if a patient's asthma score and FEV1 had not altered but he had reduced his dose of corticosteroid then this would be judged as an improvement.

The assessments of the six physicians were combined by assigning scores 2, 1, 0, −1 and −2 to the five categories and averaging the scores for every patient. The average scores were analysed by analysis of variance.

RESULTS

A total of 70 patients were submitted from 17 centres. Fourteen patients withdrew before completing six months in the trial, another five before 12 months and another five before 24 months. Seven of the patients withdrawn early did not start their injections (Table I), because they either changed their minds or proved uncooperative. The other seven withdrawals in the first six months resulted from reactions to the injections; one had received placebo injections. In one case a severe reaction occurred after the dose had been increased three times despite local reactions, contrary to the protocol. One patient required hospital treatment after a reaction to an injection. Between six and twelve months five patients withdrew. One had a severe anaphylactic reaction in month 8, one suffered a bereavement, another became pregnant and the other two gave no reason.

Table I. Number of patients in trial

No. of patients	*Treatment* A	B	C	Total
Entering trial	24	24	22	70
Withdrawals in first year				
Did not start injections	5	0	2	7
Reactions to injections	5	2	1	8
Other reasons	0	3	1	4
Completing six months	15	22	19	56
Completing 12 months	14	19	18	51
Completing 24 months	14	15	17	46

Only the 56 patients who remained in the trial for at least six months were included in the analysis. Those who withdrew later were retained in the analysis until the time of withdrawal. However, in the combined assessment at 24 months all the records were considered for patients remaining in the trial for 12 months or longer.

Completion of injection courses

If there were no local or generalized reactions a dose of 1 ml of the 0.3% extract should have been achieved in 18 weeks. In Groups A and B one patient in each took longer than 20 weeks and three in each never achieved the full dose. In the control group (C) two took longer than 20 weeks but all achieved the full dose. Information was incomplete for seven patients (three A, one B and three C).

Initial characteristics of patients

The features of the 56 patients who continued in the trial for at least six months are shown in Table II. There were some quite large differences between the treatment groups arising from the small numbers in the trial. For example, the percentage of males ranged from 37% to 73%. Since some of the factors may be of prognostic importance they were included as co-variates in the analysis in order to assess whether the response was dependent on them and to make allowance for them in treatment comparisons.

Table II. Characteristics at entry to trial of the 56 patients who completed six months

Characteristic	*Treatment*		
	A	B	C
Number	15	22	19
Male	11 (73%)	12 (55%)	7 (37%)
Aged 30 or over	10 (67%)	12 (55%)	15 (79%)
Duration of asthma, 10 years or more[*]	11 (73%)	14 (74%)	8 (50%)
Provoking factors other than house dust	4 (27%)	12 (55%)	11 (58%)
Smokers	3 (20%)	5 (23%)	1 (5%)
Off work due to asthma in last six months	7 (47%)	11 (50%)	15 (79%)
Attacks of asthma every day in last six months	6 (40%)	10 (45%)	12 (63%)
FEV_1 less than 75% predicted	9 (60%)	8 (36%)	12 (63%)
Prick test positive			
for house dust/*D. pteronyssinus* only[†]	2 (13%)	6 (27%)	5 (26%)
for one other	4 (27%)	1 (5%)	5 (26%)
for two or more others	9 (60%)	15 (68%)	9 (47%)
Mean asthma scores[‡] before treatment (range)			
Day	0.8 (0.1–1.8)	0.6 (0–1.6)	0.9 (0–2.1)
Night	0.7 (0–1.7)	0.3 (0–1.3)	0.4 (0–1.4)

[*] Not available on all patients.

[†] Weal diameter at least 3 mm more than with control solution.

[‡] Asthma scores were noted daily on the record card. The day score was: 0 = free of wheezing and shortness of breath; 1 = short of breath on hurrying; 2 = short of breath at normal pace; 3 = unable to work. The night score was: 0 = not woken by asthma; 1 = woken once or twice; 2 = awake a lot.

Asthma scores

The change in day and night asthma scores are shown in Fig. 1. For patients on corticosteroids the control group did better than those on active treatment during the first few months. The difference was significant ($P < 0.05$) for the day score in months 4–9 and for the night score in months 4–6. Later the differences between treated and controls were smaller and not significant.

For those not on corticosteroids there were no differences between treatments except that those in Group A had a better improvement in night score than those in Groups B and C. However, this difference between groups A and B was observed in the first six

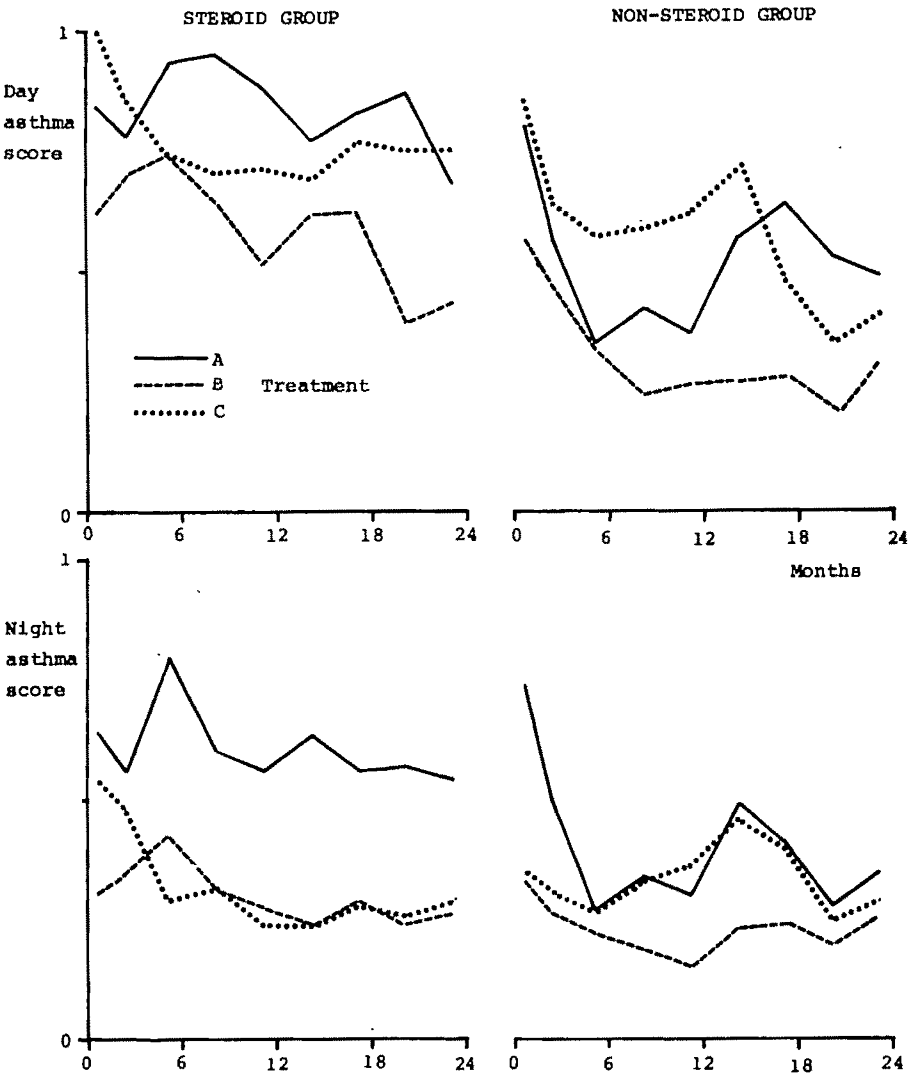

Fig. 1. Changes in day and night asthma scores over trial period for 56 patients. Day scores: 0 = free of wheezing and shortness of breath; 1 = short of breath on hurrying; 2 = short of breath at normal pace; 3 = unable to work due to asthma. Night scores: 0 = not woken by asthma; 1 = woken once or twice; 2 = awake a lot

months when treatment A and B were the same. This may have occurred because, by chance, patients on treatment A had higher initial night scores.

Changes in medication

Sodium cromoglycate was taken at some stage during the trial by 25 of the 32 patients not on corticosteroids and by 9 of the 24 on corticosteroids. Four patients (one A, one B, two C) who did not take cromoglycate during the first three months were taking it at the end of the trial. Conversely, 11 patients (four A, three B, four C) who took it during the first three months were not taking it at the end.

In the non-corticosteroid group five patients (two A, one B, two C) took steroids at some stage during the trial. In the corticosteroid group (oral or inhaled) only two patients were not taking steroids at the end and both were in the control group.

The mean number of cromoglycate capsules used initially and their subsequent changes and the mean corticosteroid dosage during the trial did not differ significantly between groups.

Use of bronchodilators

Bronchodilators were taken at some time by 49 of the 56 patients. Two patients (both B) who did not take bronchodilators during the first three months were taking them at the end. Seven patients (three A, four B) who took bronchodilators during the first three months were not taking them at the end. The difference in the proportions on active treatment and on placebo discontinuing bronchodilators (7/27 compared with 0/17) was significant ($P = 0.03$, exact test). However, two of these patients went on to inhaled

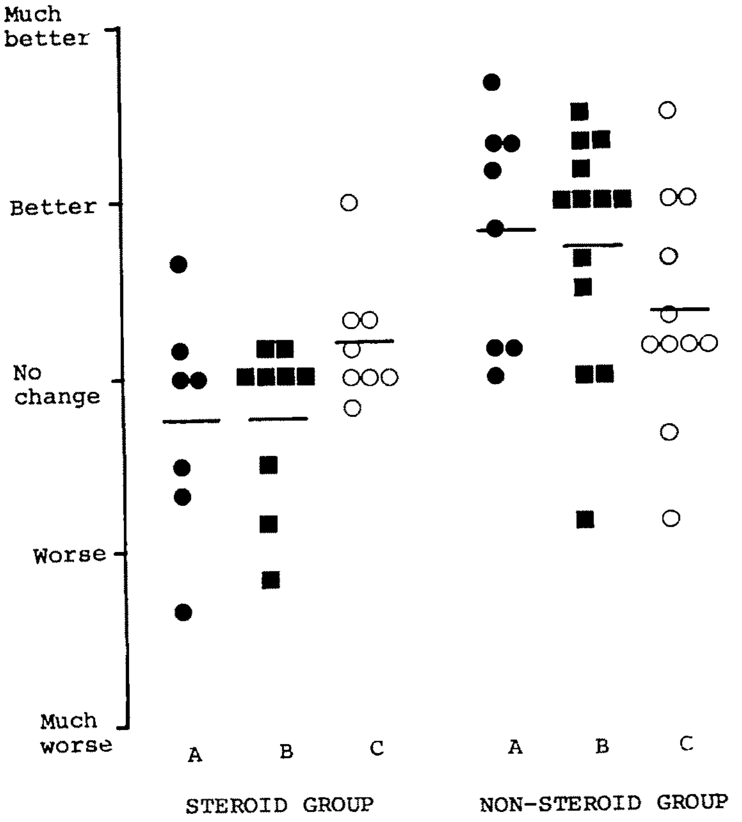

Fig. 2. Progress in trial assessed at six months by the physicians on the subcommittee

corticosteroids during the trial and two others never averaged more than one bronchodilator tablet a day at peak usage. If these are excluded the difference between the active and placebo groups becomes insignificant.

FEV_1

The mean values (% predicted) for patients were calculated and there was no statistical difference between the groups.

Combined assessment by physicians on the subcommittee

In the second method of analysis an assessment was made taking into account all factors. The results, averaged over the six physicians, are shown in Figs 2 and 3. Agreement between the physicians was good. Every one made 107 assessments and on average over the 15 physician pairs there was exact agreement in 63 cases and agreement within one category in 103 cases. Such agreement would have been expected by chance in only 35 and 84 cases respectively. Comparing the patient's own doctor's assessment with that of the six physicians, there was exact agreement in only 32 cases and agreement within one category in 80 cases. Agreement could be expected by chance in 24 and 69 cases respectively.

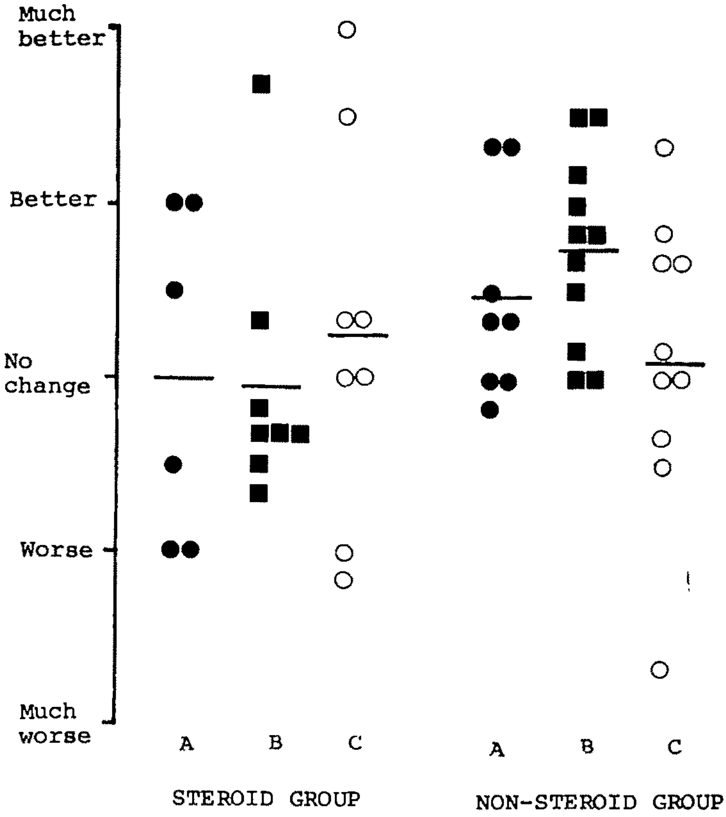

Fig. 3. Progress in trial assessed at end (24 months) by the physicians on the subcommittee

At six months, patients not on corticosteroids had done better than those on corticosteroids ($P < 0.001$). Differences between treatments were much less. In patients not on corticosteroids the treated did better than the controls and in those on corticosteroids the controls did better. These differences were not statistically significant ($0.1 > P > 0.05$).

At 24 months the differences between the groups followed a similar pattern but were smaller. The difference between patients on corticosteroids and those not on corticosteroids, and between treated and controls in the non-steroid group were both not significant ($0.2 > P > 0.1$). Those on maintenance therapy for 18 months (Group A *v* Group B) did not show any additional benefit.

None of the individual characteristics (Table II) was significantly associated with the progress at either six months or 24 months. At six months patients who had been off work due to asthma in the six months before entering the trial did better than those who had not, but the difference was not significant ($P > 0.1$). The differences between the treatment groups were assessed after making allowances for each individual characteristic separately and also for groups of characteristics simultaneously. The conclusions given earlier were unchanged except that for patients on corticosteroids the advantage from placebo injections at six months was ($0.2 > P > 0.1$). Thus, the small beneficial effect of active injections for patients not on corticosteroids was not a consequence of the differences between the groups in types of patients, but the non-beneficial effect for patients on corticosteroids could have been due to such differences.

Changes in skin and nose tests

The weal diameters following the skin test with *D. pteronyssinus* were similar for all the treatment groups at entry (average 8 mm, range 3–17 mm), and there were no significant changes.

Nasal challenge tests were not carried out on all patients and for others the results were difficult to interpret. However, within these limitations there was no noticeable effect of treatment.

Serological tests

Serological tests were carried out on entry to the trial and thereafter at six-monthly intervals. The results are summarized in Table III which shows the number of patients

Table III. Serological results

Treatment	*IgG antibody*		*Specific IgE antibody**	
	At entry	Increase by six months	At entry	Increase by six months
A	6/15	7/14	12/15	3/14
B	3/21	4/16	15/21	5/16
C	7/18	3/17	11/18	2/17

* Specific IgE was considered positive if the count exceeded 2500 per minute compared with the background count of 1500; it was considered to have increased if the count had increased by at least 500.

with IgG antibody to the mite extract or specific IgE antibody, and also the number of patients whose antibody levels had increased after six months. The proportion of patients on active injections who increased their antibody levels was twice that of control patients for both IgG and specific IgE. However, the numbers were small and the difference could have easily been due to chance. There was no association between patient's progress and the presence of specific IgE at entry.

Discussion

The number of patients recruited for the trial was small, despite repeated efforts. There seemed to be several reasons for this. Monthly attendances for two years were demanding for patients and doctors. Some were reluctant to countenance injections of a placebo for 18 months. Inhaled corticosteroids had become widely used shortly before the intake began and there may have been a dearth of patients whose asthma appeared to be due to mite allergy and who still had residual symptoms of sufficient severity to be eligible. The small numbers clearly reduce the sensitivity of the trial.

Alterations in treatment during the trial were rather frequent. Doctors were advised to reduce medicaments if the asthma improved but they were asked to avoid introducing sodium cromoglycate and corticosteroids in those not already on them, unless the indications were strong. Four patients were started on cromoglycate and five on corticosteroids during the trial and it is difficult to assess how necessary this was. Introductions and withdrawals of these drugs were evenly spread among the groups and all changes in medicines were taken into account in the physicians' assessments.

The house dust mite extract (Bencard) used in this trial was three times as strong as the commercial preparation available in Britain. This was a deliberate choice so that if no difference was found between the treated and controls it could not be attributed to low dosage. The strength of the preparation was probably responsible for the rather frequent reactions which caused the withdrawal of seven of the 43 patients receiving it. As it has also been suggested that lengthy treatment is necessary for good results (Aas 1971; Assem & McAllen 1973) one group was treated for 18 months. From one study it is suggested that in allergic rhinitis mite extract injections for 18 weeks are ineffective, but that they might produce some improvement when continued for a year (Gabriel et al. 1977).

In trials which use a treatment with substantial side-effects alongside a placebo it is impossible to maintain entirely satisfactory double-blind conditions. There were further difficulties in that there was a change to control solutions in one group after 18 weeks. It is possible that those having local reactions would have little difficulty in spotting the change but there is nothing to suggest that this affected the results.

Early trials with aqueous house dust mite extract showed some benefit (Smith 1971; D'Souza et al. 1973; Bessot et al. 1975) though no improvement was seen with an alum-precipitated extract (Newton et al. 1978) nor a short period of treatment with a depot preparation (Gaddie et al. 1976). The patients in this trial were a heterogeneous group of atopic asthmatics with a history suggesting an association between their asthma and house dust mite, and who showed evidence of house dust hypersensitivity by skin and nasal tests. It is possible that there are people whose asthma is more closely related to mite allergy who might respond to hyposensitization. We failed to identify such a group in this trial.

In our patients treatment at best produced but marginal improvement. Judged by asthma scores, patients in Group A given active material for 18 months and not taking corticosteroids showed some improvement at night. They did so during the first six months when patients in Group B failed to improve although on the same treatment. There was no difference in corticosteroid usage between the groups but more patients on active treatment discontinued bronchodilators. The combined assessments by the physicians on the subcommittee took individual changes in medication into account and found that in patients not on corticosteroids the group treated with active material did better than the controls. The difference was not significant ($0.1 > P > 0.05$) at six months and even less evident at 24 months. No additional benefit was shown by prolonging injections from 18 weeks to 18 months.

In contrast, patients on corticosteroids did slightly better on placebo injections than active material. They may represent a more severe group of asthmatics in whom the extract may have an adverse effect. But it also raises doubt about the importance of the minor improvement found in patients not on corticosteroids and given the active preparation. Forty-three patients started injections of active material and seven of these had side effects severe enough to cause the injections to be stopped; in only one case could these be clearly blamed on neglect of warning signs. Side-effects could be reduced by using weaker solutions. In the light of the marginal benefit which was found only in the patients not on corticosteroids it seems doubtful whether treatment in this form is suitable for general use.

ACKNOWLEDGEMENTS

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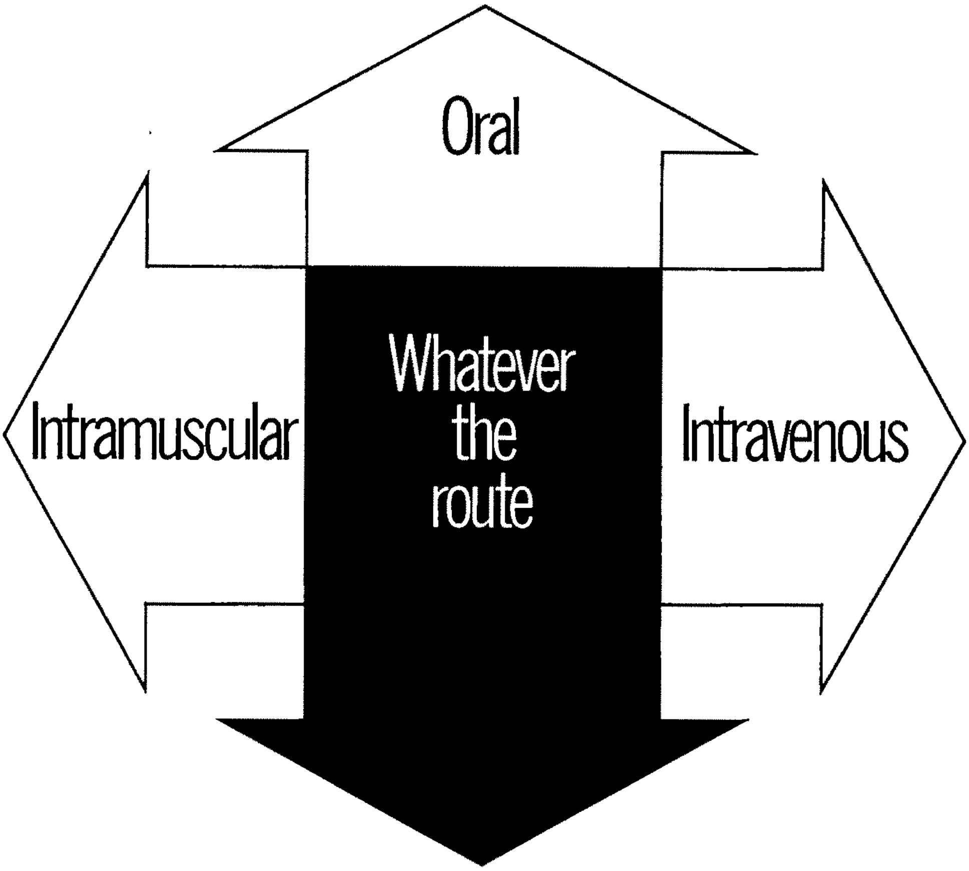

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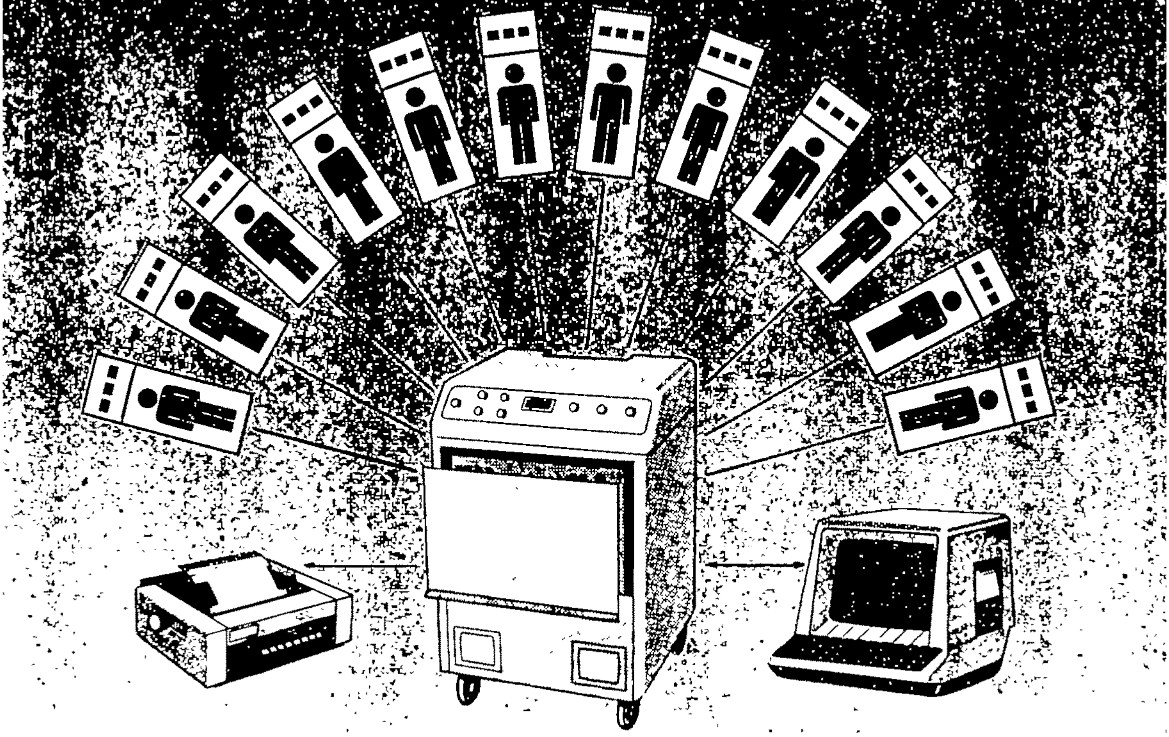

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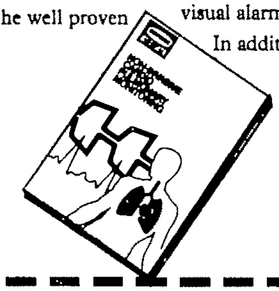

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LONG-TERM COMPARISON OF SALBUTAMOL POWDER WITH SALBUTAMOL AEROSOL IN ASTHMATIC OUT-PATIENTS

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Summary

Salbutamol dry powder was compared with salbutamol aerosol in 38 asthmatic patients. The study was double-blind and took place over six months. Salbutamol powder in a dose of 200 μg per capsule was able to control asthma as well as the aerosol, but some patients needed to increase the frequency of dosage when using the powder. The device used for powder administration, the Rotahaler, was well accepted and was preferred to the pressurized aerosol by one-third of patients. Dry powder administered by Rotahaler allows salbutamol to be given by inhalation to many patients previously using aerosols inefficiently.

INTRODUCTION

Inhalation is the preferred route of administration of β-adrenergic bronchodilator drugs in treatment of asthma because bronchodilatation is greater, more rapid in onset and longer-lasting than with oral preparations and side-effects due to systemic absorption are fewer (Walker et al. 1972; Larsson & Svedmyr 1977).

The metered-dose aerosol is well suited to most patients, but some find difficulty in synchronizing inspiration with actuation of the aerosol (Saunders 1965; Paterson & Crompton 1976). Another disadvantage of pressurized aerosols is the need for liquified gas propellants and the fluorinated hydrocarbons used for this purpose have caused environmental concern (Molina & Rowland 1974; McLean 1977) though medicinal aerosols contribute very little to total fluorocarbon atmospheric pollution. The inhalation of fluorocarbons can cause ventricular arrhythmias in animals and the possible relevance of this to man has been discussed in a recent editorial (*Lancet* 1975).

A dry powder form of salbutamol has now been developed for inhalation from a new type of inhaler (Rotahaler, Allen and Hanburys) and preliminary studies have shown it to be effective (Duncan et al. 1977; Hartley et al. 1977; Hetzel & Clark 1977).

This study was undertaken to compare the efficacy of this form of salbutamol with a conventional pressurized aerosol in the maintenance therapy of a group of asthmatic patients, and to assess its acceptability over a longer period.

Patients and Methods

Forty patients who regularly attended an asthma clinic agreed to take part in the study. All had previously shown an improvement in FEV_1 of at least 15% following the inhalation of salbutamol.

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Two patients later defaulted because of difficulties in attending the clinic and the details of the remaining 38 patients are shown in Table I.

In order to illustrate the population studied, they have been divided into atopic and non-atopic groups on the basis of two or more positive prick skin tests. Their usual therapy is also shown and this was not altered. Prior to the study, they all used a pressurized salbutamol inhaler either regularly or only as required. Patients who were incapable of using a pressurized aerosol were not included in the study as it was thought that such a group would weight the results artificially in favour of the salbutamol powder.

A double-dummy technique was used whereby patients were given two types of inhaler, only one of which contained active drug. The patients were instructed not to use their own salbutamol aerosols and were supplied instead with trial aerosols, cartridges and Rotahalers. Each time they would have normally taken their salbutamol they inhaled two puffs from the trial aerosol (containing either 100 μg of salbutamol per puff or placebo) followed by one capsule of dry powder (containing either 200 μg of salbutamol in a lactose vehicle or lactose only). The trial lasted for six months, active salbutamol being taken as dry powder for three months and as aerosol for the other three months. Patients were assessed by means of diary cards on which were recorded drug usage, the number of episodes of wheezing, symptom scores, and morning and evening peak expiratory flow rates (the best of three attempts, using a peak flow gauge (Airmed)). Symptom scores during the day were graded from 1 (confined to chair or bed by breathlessness) to 6 (no breathlessness even when hurrying) and at night from 1 (woken by asthma more than three times) to 3 (not woken by asthma). Patients attended the clinic each month not having used bronchodilators for at least six hours and FEV_1 was measured on a dry wedge spirometer (Vitalograph). They then took their trial medications under supervision, so that inhaler technique could be observed, and FEV_1 was measured again 10 minutes later. Aerosol technique was scored according to synchronization with inspiration, and Rotahaler technique according to difficulties with manipulation of the device (placing the capsule, cutting it, and locating the position for extending the chamber) and difficulties with inhalation (use of device upside down, spillage of powder and the need for more than two inhalations to remove powder). Patients' comments on the inhalers were noted and their preferences sought.

Table I. Details of patients

	Atopic	*Non-atopic*	*Total*
Number	16	22	38
Males/females	9/7	4/18	13/25
Age range (mean)	24–68 (42)	22–76 (50)	22–76 (47)
Mean duration of asthma (years)	24.1	14.8	18.8
Treatments			
Inhaled corticosteroids	11	21	32
Oral corticosteroids	7	13	20
Methyl xanthines	3	4	7
Disodium cromoglycate	1	1	2

In looking for treatment differences, only the diary card information from the third month of each treatment was compared, in order to abolish any carry-over effect. Analysis was made by Wilcoxon's rank sum test.

RESULTS

The results of diary card analysis are shown in Table II. Peak expiratory flow rates were similar during each treatment period. The normal asthmatic diurnal variation was seen, but there was no significant difference between the mean morning or evening values during the third month on each form of treatment.

Inhaler usage was slightly higher when salbutamol was in powder form and the difference was significant during the third month ($P < 0.05$).

The dosage of corticosteroids required by the 20 patients who needed them, the number of wheezing episodes and day and night symptom scores were not significantly different on each treatment. The mean monthly frequency of daytime symptom scores of 5 or 6 is shown in Table II. This reflects the severity of the asthma, as a patient with little or no disability would record 5 or 6 on many days, up to a maximum of 28 days each month.

Table II. Results of diary card analysis for months 1, 2 and 3

Results	*Salbutamol powder*			*Salbutamol aerosol*		
	1	2	3	1	2	3
Mean morning PEFR (litres/min)	292	288	282	290	292	290
Mean evening PEFR (litres/min)	321	322	312	320	322	322
Mean daily bronchodilator usage (1 capsule + 2 puffs aerosol each time)	3.4	3.5	3.6*	3.3	3.4	3.3*
Mean daily dose prednisone (mg) ($n = 20$)	8.0	7.8	7.9	6.8	6.8	7.9
Mean number of daytime wheezing attacks	0.6	0.5	0.6	0.6	0.6	0.9
Mean monthly frequency of daytime symptom scores 4, 5 or 6	19	19	18	18	18	16

* $P < 0.05$. No other differences were significant.

Base-line FEV_1 levels at clinic visits were similar on salbutamol powder and aerosol and there was a similar response to inhalation of salbutamol in the clinic. Several subgroups were examined, including those with the poorest lung function (FEV_1 less than 50% of the predicted value) (11 patients) and patients who preferred using the Rotahaler (13 patients). In none was the powder superior to the aerosol at the dose used. The responses to aerosolized salbutamol were a little better than to powder, but not significantly so.

In addition to studying the value of salbutamol powder in controlling asthma, we were interested to see how well patients accepted the new powder and inhaler. All tolerated the powder well, although many did not like the extra manipulation required to use the Rotahaler; 25 (66%) preferred the aerosol, all because of its greater convenience. However, 13 patients (34%) preferred the Rotahaler, eight stating that they were more certain of the dose they were getting, five that they were better at using it and one volunteering that it was less liable to abuse.

Only 11 of the 38 patients (29%) used both devices correctly at every visit: 18 patients (47%) had faulty aerosol technique on at least one occasion, and 19 patients (50%) had faulty technique with the Rotahaler at least once. Eight patients (21%) had faulty technique with both devices. Faults with use of the Rotahaler are shown in Table III. The most common fault was use of the device upside down, which can allow powder to spill out of the air inlet slots. Difficulty in finding the correct position for extension of the device prior to inhalation was also a common problem. Slight powder loss occurred on 12 occasions with nine patients.

Table III. Faults with Rotahaler technique

Fault	*Occurrence*
Difficulty placing capsule in inhaler	3 patients on 6 occasions
Difficulty in cutting capsule	5 patients on 9 occasions
Difficulty in extending device	7 patients on 16 occasions
Inhaler upside down	9 patients on 18 occasions
> three inhalations to remove powder	3 patients on 6 occasions
Loss of powder before inhalation	9 patients on 12 occasions

DISCUSSION

Some asthmatic patients have been denied effective use of selective β-adrenergic agonists by inhalation because of inability to use a pressurized aerosol correctly. Paterson and Crompton (1976) have shown that most patients who are unable to use pressurized aerosols can use a Spinhaler (Fisons) to inhale disodium cromoglycate. This device does not have to be triggered, the powder being drawn into airways by inspiration. The Rotahaler acts on a similar principle, except that the capsule containing powder is cut in half rather than punctured by the device, and very low inspiratory flow rates are required to discharge the powder (Hallworth 1977).

We found that one-third of our patients preferred the Rotahaler to a pressurized aerosol and were prepared to tolerate the slight loss of convenience involved in loading the device. Faulty inhaler technique was quite common with both the aerosol and the Rotahaler. However whereas faulty technique with the Rotahaler usually merely increases the time taken to use it, faulty technique with pressurized aerosols always results in an unquantifiable loss of bronchodilator delivered to the airways. The only serious fault with the Rotahaler was when powder loss occurred prior to inhalation due to excessive manipulation or use of the device upside down. This should occur less commonly with the commercially available devices which are clearly marked than with the plain white trial inhalers we used in this study. We found that Rotahaler blades became blunt after two or three months of use, and doctors prescribing this form of treatment should remember that not only do supplies of capsules need to be replaced but so too does the inhaler.

We have shown that there was no significant difference in ventilatory function or in symptom scores between our group of out-patient asthmatics when treated with salbutamol from the conventional aerosol or with dry-powder salbutamol from a Rotahaler. In the dose we used, 200 μg, there was a slight increase in the frequency of inhaler usage when the drug was in powder form. This was significant during the third month on each treatment but not during the first two months. In most patients such a small difference, even if genuine, is not likely to be clinically important. In two of our patients, however, the difference was striking as they needed to use their inhalers twice as often during the three months when it transpired that they were using dry salbutamol powder. Their inhaler requirements fell afterwards when again using the aerosol. Although several patients said that they felt better during the three-month period of powdered salbutamol, there was no objective proof of this from any aspect of diary card analysis.

Our choice of dose was made after acute studies by others had shown that 200 μg of salbutamol in powder form was not significantly inferior to the same dose in aerosol form, (Hartley et al. 1977; Hetzel & Clark 1977). Duncan et al. (1977), however, found that 200 μg of salbutamol aerosol produced significantly greater bronchodilatation in terms of mean average increase in FEV_1 (area under the curve) than 200 μg of powder, though not in terms of maximum improvement in FEV_1. This may explain why there was no significant difference in the improvement of FEV_1 following salbutamol which we observed at each clinic visit, as we were not looking at the duration of action of each treatment on these occasions. If there is a small difference in effect of equal doses of salbutamol when given by aerosol or dry powder it is probably related to particle size. Hallworth (1977), using a Multistage Liquid Impinger, found the delivery of particles which were likely to enter the lungs from a Rotahaler to be only half that which could be achieved from an aerosol. Particles of dry salbutamol sulphate powder are 1–5 μm in size, while those of the lactose carrier are much larger. It is likely that clumping of particles occurs, leading to more deposition of drug in the pharynx and upper airways (Muir 1974), and hence less effective bronchodilatation.

Our study has shown that most asthmatic patients would obtain adequate control from 200 μg of salbutamol powder instead of their aerosol, but a few require a larger dose. It is therefore reasonable to have available both 200 μg and 400 μg capsules when considering substitution of the standard salbutamol aerosol (100 μg per puff).

We conclude that the Rotahaler is effective and acceptable to use. A further advantage is the lack of fluorocarbon propellants, which might make excessive usage of the inhaler less hazardous (Editorial, *Lancet* 1975) and has theoretical ecological advantages. The device should help patients who are at present using pressurized aerosols inefficiently or who have little confidence in their ability to use them properly on all occasions. It should also help very young or elderly patients, for whom relatives can prepare the inhaler and supervise inhalation.

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CONTINUOUS AND INTERMITTENT SALBUTAMOL TABLET ADMINISTRATION IN ASTHMATIC CHILDREN

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Summary

We studied 22 asthmatic children aged seven years two months to thirteen years eight months over a four-month period. Each child received two months continuous and two months intermittent salbutamol tablets using a double-blind cross-over technique. No significant clinical differences were found between the two treatment regimens as judged by daily diary card scores. Daily PEFRs (both a.m. and p.m.) were significantly higher ($P < 0.05$) when the children were receiving continuous salbutamol and this was more obvious in the eleven children under ten years old. Lung function tests performed monthly in hospital showed no significant differences between the two treatment regimens.

INTRODUCTION

Oral salbutamol is an effective bronchodilator for asthma in children. It may be given regularly three or four times daily but is often administered intermittently when wheezing occurs. Previous work in adult asthmatics has failed to show tolerance to salbutamol after continual administration for four weeks (Sims 1974; Bhatia & Davies 1975). In a recent study on six healthy adult volunteers salbutamol aerosol given for four weeks, however, produced a progressive loss of airways responsiveness to both inhaled and intravenous salbutamol (Holgate et al. 1977).

No studies have been carried out in children comparing the clinical effectiveness of continual salbutamol tablet administration with salbutamol tablets given only when symptoms occur. The present study was therefore designed to compare these regimens.

Materials and Methods

The 22 patients (twelve boys, ten girls) who took part in the study were aged from seven years two months to thirteen years eight months (mean ten years). Eleven children were under ten years old. At the beginning of the study two were receiving no therapy; eight salbutamol alone; five salbutamol and sodium cromoglycate; and seven salbutamol and beclomethasone dipropionate.

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Patients were selected for study if they were symptomatic despite their current therapy. The age of onset of wheezing ranged from 18 months to five years. Eleven children had eczema and four allergic rhinitis. There was a family history of asthma, eczema or hay fever in 17.

Each child received one white tablet four times daily for four months. For two consecutive months, these tablets were salbutamol and for the other two consecutive months placebo, the order being previously allocated at random under double-blind conditions according to a predetermined design. If the patient was previously taking sodium cromoglycate or beclomethasone dipropionate, these were continued. If symptoms occurred despite the above therapy the child was instructed to take extra pink tablets up to a maximum of six daily. The pink tablets were always active salbutamol tablets. The eleven children under ten years received 2 mg salbutamol tablets whilst the eleven children ten years or older received 4 mg salbutamol tablets whether administered as white or pink tablets.

Each child completed a daily record of cough and wheeze symptoms both day and night. Possible scores for wheezing ranged from 1 ('terrible') to 6 ('very well') and for cough from 1 ('frequent, distressing') to 4 ('none'). Daily morning and evening peak expiratory flow rates (PEFRs) were recorded at home using an Air-Med Peak flow gauge and a daily record was kept of all medications received. At the beginning of the study and at monthly intervals throughout, lung function tests were performed on all patients. These tests were PEFR, forced vital capacity (FVC) and forced expiratory volume in 0.75 sec ($FEV_{0.75}$); also thoracic gas volume (TGV) and airways resistance (R_{aw}) using the plethysmographic technique (Dubois et al. 1955). Statistical analysis was applied to diary card scores, daily home PEFRs, the number of salbutamol tablets used and laboratory lung function tests for each treatment period. To avoid any carry-over effect, analysis was only applied to the second month of each treatment period.

RESULTS

All the children completed the study.

Comparing the results of all children, regardless of age, we were unable to show any statistical evidence of treatment difference in the daily asthma or daily cough score data. There were, however, more symptom-free days when the children were taking continuous salbutamol and although this trend did not reach statistical significance it was also present when the children under ten years and those ten years and over were examined separately (Table I).

The mean daily number of extra pink salbutamol tablets taken per person was considerably less in the children receiving continuous therapy but the total mean number consumed per person was 4.4 during continuous and 1.1 during intermittent therapy. There was no statistical difference in the pattern of tablet consumption between the children under ten years and those ten years or above (Table I).

For the group as a whole, continuous administration of oral salbutamol produced significantly greater mean home PEFRs (a.m. and p.m.) than intermittent administration ($P < 0.05$). This was more obvious in the children under ten years old, significant levels being $P < 0.02$ and $P < 0.005$ for a.m. and p.m. respectively.

There was no significant difference between continuous and intermittent therapy on the monthly lung function tests, either looking at the whole group or examining the younger and older age groups separately (Table II).

At the end of the study the parents were asked during which two months they thought their children had least symptoms from their asthma. Ten parents chose the continuous and seven parents chose the intermittent therapy period. Five parents thought there was no difference between the two treatment periods.

Table I. Differences between continuous and intermittent salbutamol regimens

	Children under 10 years (*n*=11)		*Children 10 years and above* (*n*=11)		*All children* (*n*=22)	
	Continuous salbutamol	Intermittent salbutamol	Continuous salbutamol	Intermittent salbutamol	Continuous salbutamol	Intermittent salbutamol
Asthma score = number of symptom-free days per month						
Day	22	17.5	17.5	15.5	20	16
Night	25.5	21.5	21.6	19	24	20
Cough score = number of symptom-free days per month						
Day	16.5	11.4	20.7	16.2	19	14
Night	15.3	13.2	23	18.7	19	16
Total mean number of salbutamol tablets taken daily	4.55	0.9	4.35	1.2	4.4	1.1
Mean daily PEFR (litres/min)						
a.m.	190	162	244	220	216	192
p.m.	208	171	261	238	234	205

Table II. Summary of hospital lung function tests (mean for all 22 children)

Lung function test	*Continuous salbutamol*		*Intermittent salbutamol*		*Predicted value (for height)*
	1	2	1	2	
PEF (litres/min)	222	187	178	188	282
FEV 0.75 (litres)	1.4	1.2	1.1	1.2	1.8
FVC (litres)	2.0	1.8	1.8	1.8	2.3
TGV (ml)	1854	1976	1973	2034	1532
R_{aw} (KPa/litre/sec)	0.37	0.42	0.52	0.46	0.28

DISCUSSION

We were unable to show any significant clinical differences between continuous and intermittent therapy in these children. Admittedly, the introduction of continuous placebo tablets created an artificial therapeutic situation but we thought it important to conduct the study under double-blind conditions and were therefore unable to avoid this problem. All the children tolerated the salbutamol tablets well. In the children under ten years, cough was more troublesome than wheeze and may well be a useful indicator of airways obstruction in this age group. Similar results were obtained in a recent long-term study of asthmatic children under five years old (Hiller et al. 1977). Children notoriously underestimate the severity of their asthma on symptom scores and it is possible that PEFR values are more useful indicators of therapeutic success. Continuous salbutamol administration produced significantly higher daily PEFRs than intermittent therapy and this was more obvious in the younger children. We considered the better values in the children under ten years were because these children had suffered from asthma for a shorter time than the older children and that their asthma was probably less severe. This was supported by the fact that the mean PEFR in the young children was 69% of the predicted value whereas it was only 58% of the predicted value in those children ten years or over. Virtually identical values were obtained for $FEV_{0.75}$ (69% and 56% respectively). The mean TGV was 116% of the predicted value for the younger children and 128% in those ten years and over. As judged by their therapy before the study, however, the two age groups were very similar in that four of the seven children taking beclomethasone dipropionate, two of the five children receiving sodium cromoglycate and four of the eight children taking salbutamol alone were ten years or older. All the results have also been analysed for each patient separately but no further useful information has been obtained.

The main conclusions from this study are:

1. Continuous salbutamol tablet therapy, given four times daily at the conventional dosage, has no clinical advantage over salbutamol tablets given as required.
2. Daily PEFRs are marginally better in asthmatic children receiving continuous salbutamol therapy and this effect is more pronounced in children under ten years old.

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NEEDLE BIOPSY OF THE PLEURA IN NIGERIA

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Summary

The results of needle biopsy of the pleura carried out on 200 patients are presented. Biopsy was diagnostic in 60% of tuberculous pleural effusions and in 74% of cases of malignant effusions. The histological appearance of chronic fibrosis was seen in 34%, of which half were subsequently found to have tuberculosis.

INTRODUCTION

Biopsy of the parietal pleura was originally carried out by thoracotomy (Sutcliffe et al. 1954). The first report of needle biopsy of the parietal pleura was that of De Francis et al. (1955) who used a Vim-Silverman needle to establish a diagnosis of tuberculosis in two of the six patients with pleural effusion. The technique of punch biopsy of the pleura was described by Abrams in 1958 and the first report of its use in Nigeria was that of Lucas and Mainwaring in 1963.

The present study examines this technique in the diagnosis of pleural effusion in a community where tuberculosis is still prevalent and is known to be the commonest cause of pleural effusion (Onadeko 1977). The diagnosis of tuberculosis in such patients by other methods such as isolation of *Mycobacterium tuberculosis* on culture of sputum or pleural fluid is rarely possible.

Materials and Methods

Pleural biopsy was carried out using the Abrams needle at University College Hospital, Ibadan. Two hundred patients who had this investigation were included in this study. The biopsy was repeated in nine patients in whom the histological appearances on initial biopsy were inconclusive.

RESULTS

The age of the patients ranged from 12 to 70 years with most in the age group 21–30 years. Of the 200 pleural biopsies 62 (31%) showed the histological appearances of tuberculosis and 20 (10%) showed malignant infiltration. A histological diagnosis of fibrinous pleurisy was made in 20 cases (10%) and 'chronic fibrosis' was reported histologically in 68 patients (34%). In 30 cases (15%) the appearances were inconclusive.

Table I shows the pleural biopsy findings in relation to the final clinical diagnosis. Pleural biopsy was diagnostic in 60% of cases of tuberculous pleural effusion and in 74% of cases of malignant effusion. Thirty-seven (54%) of the 68 cases with a histological report of chronic fibrosis in pleural biopsy were subsequently diagnosed as having

Table I. Pleural biopsy findings in relation to final diagnosis

Final clinical diagnosis	*Biopsy*	*Pleural biopsy diagnosis*				
		Tuberculosis	Malignancy	Acute fibrinous pleuritis	Chronic (dense) fibrosis	Inconclusive
Tuberculosis	115	62	—	4	37	12
Malignancy	27	—	20	—	4	3
Pneumonia	23	—	—	13	8	2
Congestive cardiac failure	15	—	—	1	8	6
Nephrotic syndrome	4	—	—	—	3	1
Septicaemia	1	—	—	—	—	1
Constrictive pericarditis	2	—	—	—	2	—
Endomyocardial fibrosis	1	—	—	—	—	1
Liver cirrhosis	2	—	—	—	1	1
Abscesses (splenic, amoebic etc.)	3	—	—	1	1	1
Others	5	—	—	1	3	1
Cause unknown	2	—	—	—	1	1
Total	200	62	20	20	68	30

tuberculous effusions by other means such as demonstration of *Mycobacterium tuberculosis* in sputum or pleural fluid, biopsy of liver or lymph nodes, bronchoscopic biopsy, thoracotomy or autopsy. Of the 20 cases with a histological diagnosis of fibrinous pleurisy on biopsy 13 (65%) turned out at final diagnosis to have a pneumonic pleural effusion. A repeat needle biopsy on nine of the 15 patients who had inconclusive appearances at initial biopsy showed malignant infiltration in five.

DISCUSSION

The results of needle biopsy of the pleura in this series confirm its value in the diagnosis of the cause of pleural effusions especially when tuberculous or malignant. Needle biopsy was helpful in diagnosis of 60% of our patients with tuberculous effusions and 74% with malignant effusions. Hampson and Karlish (1961) reported diagnostic biopsies in 75% of tuberculous and 62% of malignant effusions, and similar results were given by Mestitz et al. (1958). In a previous study on Nigerian patients Lucas and Mainwaring (1963) obtained biopsies diagnostic of tuberculosis in 60% of cases, but found the method less helpful in the diagnosis of malignant effusion which they considered to be very rare in Nigeria.

In the present series 54% of cases with histological appearances of chronic fibrosis in biopsy specimens were eventually found to be tuberculous. In the report by Lucas and Mainwaring (1963) 50% of cases with a histological diagnosis of chronic non-specific inflammation were later shown to have tuberculosis and similar observations were made by Mestitz et al. (1958). We would therefore suggest that if feasible the biopsies should be repeated on all cases showing this histological appearance and that tuberculosis should be considered as a cause especially in regions of high prevalence. A repeat biopsy should also be performed if inconclusive histological appearances are seen on the initial specimen. In our hands this led to a diagnosis in five of the nine cases who had a second biopsy.

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A SURVEY OF THE LONG-TERM EFFECTS OF TALC AND KAOLIN PLEURODESIS

Research Committee of the British Thoracic Association
and the Medical Research Council Pneumoconiosis Unit*

Summary

Of 210 patients who underwent pleurodesis with iodized talc or kaolin 14 to 40 years previously, all but 11 were traced. There was no increased incidence of lung cancer and no case of mesothelioma.

Introduction

Exposure to high concentrations of talc dust in mining and processing in the USA has been shown to cause pulmonary fibrosis and a four-fold increase in the incidence of malignant tumours of the lung and pleura (Kleinfeld et al. 1967). However, this dust contained other silicates including tremolite and anthophyllite and the incidence of these malignant tumours fell and approached the expected mortality when dust levels were reduced (Kleinfeld et al. 1974). In a controlled study of Italian talc miners and millers exposed to a very pure type of talc Rubino et al. (1976) were able to show a lower than expected incidence of lung cancer, although the mortality rate amongst the miners exceeded the norm because of the high incidence of pneumoconiosis (silicosis) with or without tuberculosis. In Great Britain Henderson et al. (1971) described talc particles in association with carcinoma of the ovary and cervix, confirmed later by analytical electron microscopy (Henderson & Griffiths 1975). Jackson and Bennett (1973) reported a chest wall tumour of adenocarcinomatous type developing within three years of iodized talc pleurodesis for recurrent spontaneous pneumothorax but it is unlikely that the talc played any causative role in the development of this tumour. Animal studies using inhalation and intrapleural injection of an Italian cosmetic talc have failed to demonstrate a carcinogenic effect (Wagner et al. 1977).

Talc, which is mainly a hydrated magnesium silicate, is marketed in different grades, the higher grade being used for cosmetic and pharmaceutical purposes and the others in industry (Hildick-Smith 1976). Cosmetic talc consists of flake-like particles and is largely free of the long thin fibres of asbestos-like minerals (such as tremolite, actinolite and anthophyllite) which are closely related to it in the natural state. These contaminate some industrial talcs, however, and are possibly responsible for the fibrogenic and carcinogenic effects already referred to. In Britain talc has been used by intrapleural poudrage since 1935 to induce pleurodesis, usually for treatment of recurrent spontaneous pneumothorax. A follow-up of such patients should reveal any possible carcinogenic effects of talc and a subcommittee was set up by the British Thoracic Association and Medical Research Council Pneumoconiosis Unit to organize a survey.

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* Members of the subcommittee were A. G. Chappell (chairman), A. Johnson (coordinator), J. Charles, J. C. Wagner, R. M. E. Seal, G. Berry and D. Nicholson.

Methods

In order to obtain a large number of index cases 11 thoracic centres were approached but only three were able to participate: Sully, Brompton and Harefield Hospitals. At each centre medical record indexes and surgical registers were reviewed and the notes scrutinized to identify patients who had received pleurodesis with talc or a like mineral such as kaolin (china clay, hydrated aluminium silicate) before January 1961 so that a minimum observation period of 14 years was possible. Tracing the patients proved a difficult and lengthy task. Methods used included direct written approaches to patients and general practitioners, family practitioner committees, the Office of Population Censuses and Surveys (OPCS) and foreign embassies. A large number of patients would have remained untraced without further assistance from two 'field' workers with experience of epidemiological studies who cross-checked information for accuracy and made visits to discover the present state of index cases not traced by letter.

The results were assessed by comparing the number of observed deaths with the number expected by the subject-years method (Case & Lea 1955) multiplying years of risk by death rates. The death rates for England and Wales were taken from tables compiled for studies of this kind (Institute of Cancer Research 1976). These tables give age-specific death rates with age in five-year groups and also calendar year in five-year groups up to 1966–70. The study extends beyond 1970 and the rates for 1966–70 were used for the later years. Deaths from all causes and also from cancer of the lung and pleura have been considered. Excess mortality has been tested by treating the observed number as a Poisson variable with expectation equal to the expected number.

RESULTS

Two hundred and ten cases were collected from the three centres (Table I). The Sully patients, many of whom had chronic lung disease such as chronic bronchitis, emphysema and pneumoconiosis, received intrapleural kaolin as treatment for spontaneous pneumothorax between 1956 and 1960. All the Brompton and Harefield patients received intrapleural talc over half having been treated before 1945. In 22 Brompton and 70 Harefield patients iodized talc was used to produce pleurodesis in patients with bronchiectasis and other non-malignant disorders before lung resections.

Table I. Outcome of the study

Hospital	*No. of patients (males)*	*Contacted, alive and well*	*Untraced but believed alive*	*Emigrated and untraced*	*Dead (lung cancer in parentheses)*
Sully	63 (50)	45	—	—	18
Brompton	43 (24)	26	—	3	14 (1)
Harefield	104 (54)	81	2	6	15 (2)
	210 (128)	152	2	9	47 (3)

One hundred and fifty-two patients have been contacted and are well whilst a further two are thought to be alive (OPCS) but have not been traced (Table I). Follow-up data are available on nine emigrants for periods ranging from 14 months to 24 years but attempts to locate them have failed.

There were 47 deaths including three from lung cancer (Table II). Two patients with lung cancer had a tumour on the side opposite to the pleurodesis with intervals of 18 months and 19 years between pleurodesis and death. The third case was a 61-year-old

Table II. Observed and expected mortality

Hospital	*Sex*	*All causes**		*Lung cancer†*	
		Obs.	Exp.	Obs.	Exp.
Sully	Men	18	9.1	0	0.84
	Women	0	0.8	0	0.03
Brompton	Men	9	3.4	1	0.36
	Women	5	4.0	0	0.06
Harefield	Men	11	7.1	2	0.72
	Women	4	4.6	0	0.13
Total		47	29	3	2.14

* $P<0$ 01.

† $P>0.3$.

man with an oat cell carcinoma who died 32 years after pleurodesis. The site of the carcinoma is not known and at autopsy no tumour was found, but he had received radiotherapy. Although lung cancer deaths were no greater than expected, there was a significant excess of observed over expected mortality for all causes (the two untraced patients were assumed to be alive for the purposes of this calculation).

Table III shows that although follow-up was longer than 15 years in the majority of patients, 36 deaths occurred within 15 years of pleurodesis. The observed deaths in these three quinquennia were significantly more than expected. The probable explanation is the already high incidence of respiratory disease in these patients at the time of pleurodesis for 21 of the deaths were due to respiratory causes.

Table III. Duration of follow-up after pleurodesis

Duration of follow-up (years)	*Deaths*	*Others*
0–4	16	4*
5–9	9	2*
10–14	11	5†
15–19	6	70
20–24	2	7
25–29	0	3
30–34	2	45
35–39	1	27
Total	47	163

* Emigrated.

† Includes one emigrant.

DISCUSSION

This study was devised in 1974 because of the suggestion that talc might be carcinogenic. Later reports quoted in the introduction have not supported this view and asbestos-like contaminants were possibly responsible for the early reports of an increased incidence of carcinoma. Strict standards for the manufacture of cosmetic talc have been adopted only in recent years (Editorial, 1977). We have been able to ascertain that talc B.P.

was used at Brompton and Harefield Hospitals even before 1945. Indian Finex has been used extensively for this preparation in the past and is unlikely to have contained any fibrous amphiboles but we have no idea of the composition of other B.P. talcs over the past 40 years (Pooley 1978). It was decided to include patients treated with kaolin because of its chemical similarity to talc and its propensity for producing pulmonary fibrosis after prolonged and heavy exposure, even though no carcinogenic effect has been ascribed to the mineral. All the Sully patients received kaolin rather than talc for their pleurodesis, but even if they are excluded from the analysis of lung cancer deaths (Table II) the ratio of the observed to expected incidence is still not significant ($P = 0.14$).

Tracing of patients proved very difficult, particularly those from Brompton and Harefield cases, over half of whom were treated prior to 1945. No attempt was made to examine or X-ray the patients, who were scattered throughout the country. It was felt that this would prolong the study and prove unrewarding as very few asymptomatic cases of mesothelioma would have been expected, for Elmes and Simpson (1976) in their study of 327 cases found a mean interval between onset of symptoms and arrival at hospital of only 3.4 months.

We have therefore found no increased incidence of lung cancer and no case of mesothelioma in the series of 210 patients, 88 of whom have been followed for between 15 and 30 years and 75 for 30–40 years after pleurodesis.

ACKNOWLEDGEMENTS

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ULTRASTRUCTURAL STUDY OF PULMONARY PLASMA CELL GRANULOMA—REPORT OF A CASE

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Summary

Electron microscopy of a tumour diagnosed as a pulmonary plasma cell granuloma showed that the tumour was composed of plasma cells, fibroblasts, histiocytes and other inflammatory cells. The plasma cells were mature, with abundant endoplasmic reticulum. Fibroblasts contained multiple lipid droplets and intracytoplasmic inclusions. The relationship between plasma cell granuloma and lesions believed to be related is discussed.

INTRODUCTION

Since the first report by Childress and Adie in 1950, Spyker and Kay (1956), Nyman (1963) and Bahadori and Liebow (1973) have described the clinical and pathological manifestations of pulmonary plasma cell granuloma. Plasma cell granuloma is morphologically different from plasmacytoma. Ultrastructurally, most of the plasma cells in plasma cell granuloma are mature and do not display proliferative or invasive growth. In this paper the case of a patient in whom surgical removal of a plasma cell granuloma was not followed by recurrence is reported and its ultrastructural findings are discussed.

Case Report

A 27-year-old man was admitted to Kyushu University Hospital in September 1971 because of a solitary lesion in the right lung on routine chest radiographic examination (Fig. 1). He was symptom-free and there were no episodes of pulmonary infection in the past. Tomographic films showed a sharply defined, round mass which slightly compressed a branch of the right upper lobe bronchus on the bronchogram. No abnormal findings were seen with fibreoptic bronchoscopy. Sputum cytology revealed no atypical cells and culture for tubercule bacilli was negative. Total serum protein was 86 g/litre and gammaglobulin was 22%. Other laboratory data were normal.

The patient underwent a thoracotomy and a right upper lobectomy was performed. There was an oval-shaped, firm tumour measuring 36 × 34 × 30 mm occupying the upper lobe. The tumour was well-encapsulated without any gross evidence of infiltration into surrounding tissues. There was no abnormal enlargement of hilar lymph nodes. The cut surface was even and yellow. No necrotic areas were noted. Postoperatively the patient did well and was discharged from the hospital in March 1972. There was no evidence of recurrence on the four-year follow-up chest radiograph.

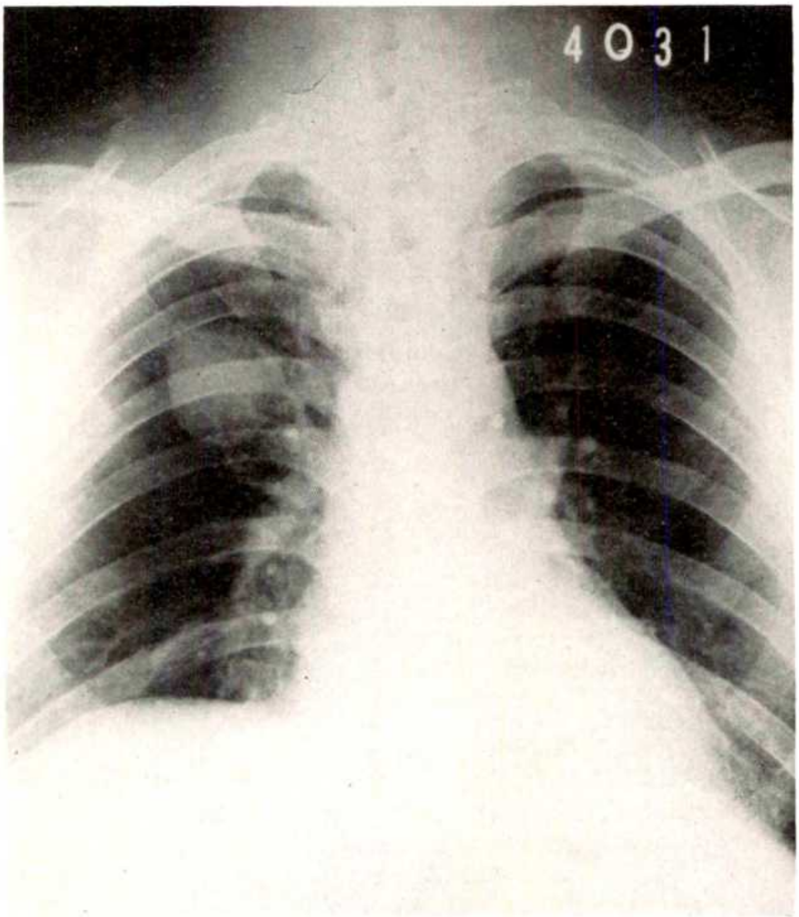

Fig. 1. The chest radiograph showing a round lesion in the right upper lobe.

LIGHT AND ELECTRON MICROSCOPY

Thick sections of the tumour were fixed in 10% formalin and were examined under the light microscope. Small specimens were fixed in 2% glutaraldehyde and then in 1% osmium tetroxide. After the specimens had been embedded in epoxy resin, thin sections were made by Porter Ultramicrotome. Suitable areas were selected under the light microscope and then ultra-thin sections were prepared. These sections were stained with uranyl acetate and lead citrate. Observations were performed with a JEM 100-B type electron microscope.

Under light microscopy the tumour was well-encapsulated except in one area where inflammatory cells infiltrated the surrounding lung parenchyma. The tumour consisted mainly of plasma cells which possessed characteristic nuclei with a spoke wheel distribution of chromatin material. In areas where there was a particularly heavy accumulation of plasma cells, typical Russell bodies were found (Fig. 2). Throughout the lesion fibroblasts and fibrocytes were mixed with plasma cells (Fig. 3) and these fibroblasts stained

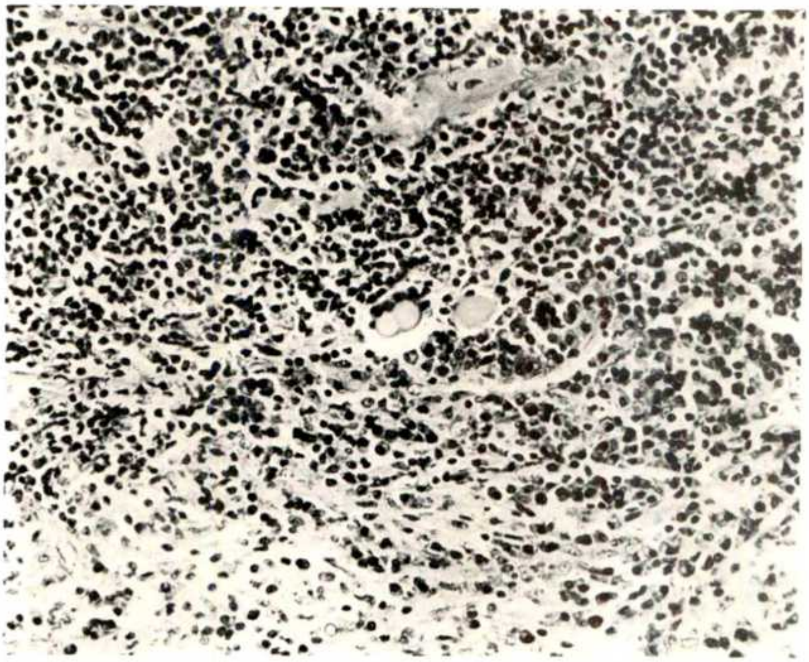

Fig. 2. The tumour composed of many plasma cells and a few fibroblasts and histiocytes. Russell bodies are seen in the centre of the figure. H & E ×280

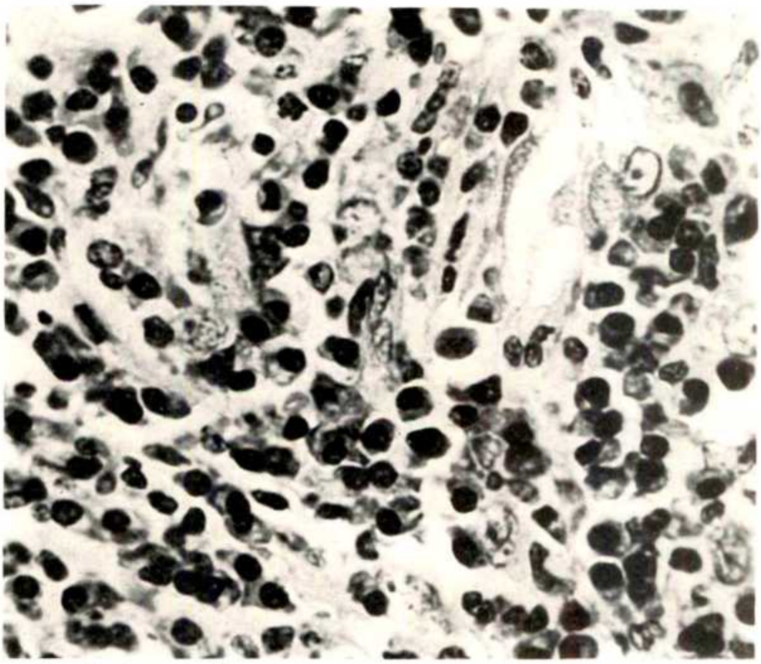

Fig. 3. Accumulated plasma cells, and other inflammatory cells (fibroblasts and histiocytes). H & E ×770

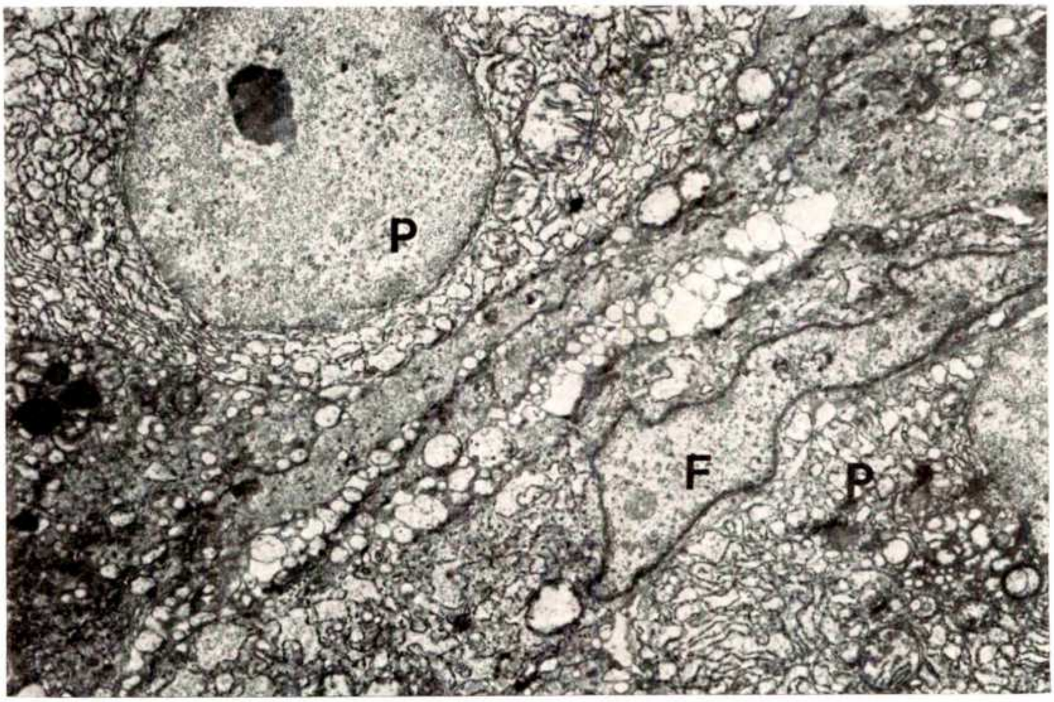

Fig. 4. Abundant rough endoplasmic reticulum in plasma cells. P = plasma cell; F = fibroblast. × 2100

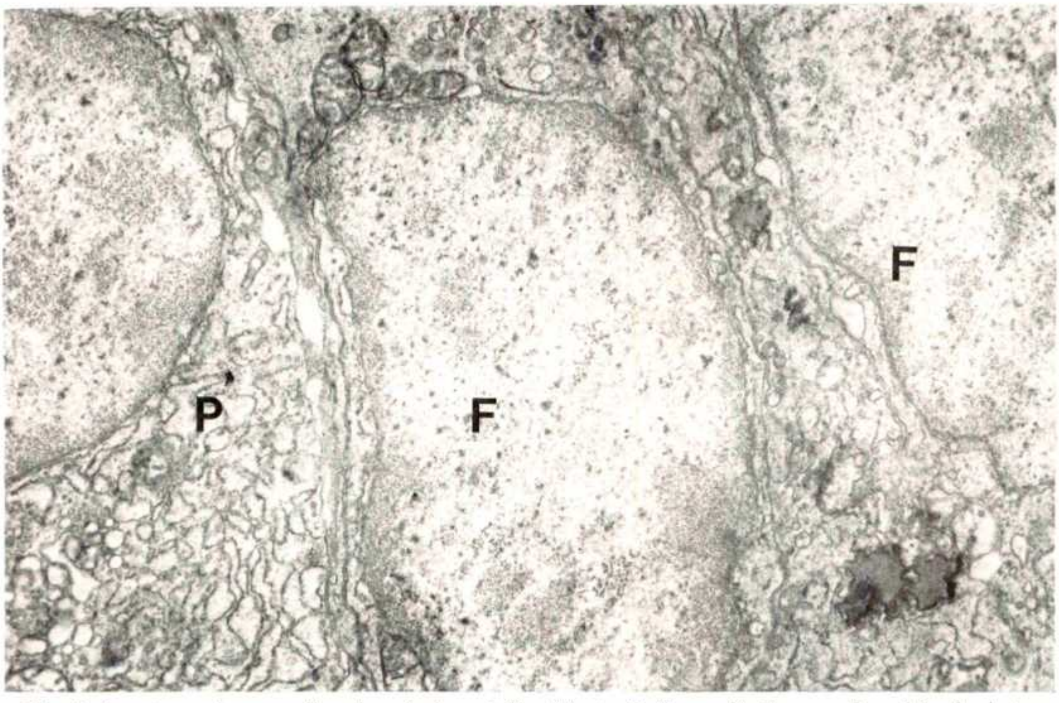

Fig. 5. A mature plasma cell and oval-shaped fibroblasts. Collagen fibrils were found in the intercellular spaces among these cells. P = plasma cell; F = fibroblast. × 3500

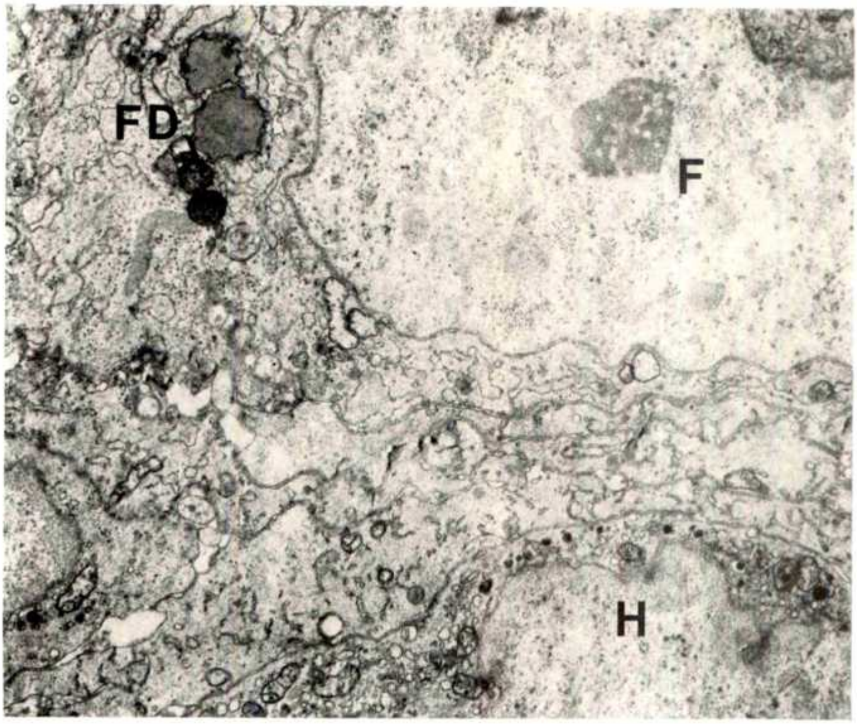

Fig. 6. A fibroblast showing the irregular nuclear margin and variously shaped fatty droplets, and a histiocyte with a few lysosomal bodies in the cytoplasm. F = fibroblast; H = histiocyte; Fd = fatty droplet × 4000

positively with Sudan III. Histiocytes, lymphocytes and reticular cells were also present but not so abundant. Only a few mast cells were found. A histological diagnosis of plasma cell granuloma was made on the basis of the predominance of plasma cells.

Electron microscopy showed that the tumour was composed of various non-epithelial cells. The predominant cells were mature plasma cells, characterized by abundant rough endoplasmic reticulum and rich ribosomal material (Fig. 4). These cells had round nuclei with dense clumps of chromatin material at the margins and solitary nucleoli. Mitochondria were not abundant and the Golgi complexes appeared to be normal. Some of the rough endoplasmic reticulum occasionally showed saccular or vesicular dilatation. Nuclear inclusions could not be found. Only a few immature plasma cells with less abundant endoplasmic reticulum were seen. Plasma cells with Russell bodies were seen under light microscopy but could not be found in any of the examined areas.

Spindle- or oval-shaped cells containing abundant intracytoplasmic fatty droplets were seen mingled with plasma cells in all the sections (Figs 5, 6, 7). These cells were labelled fibroblasts, because they were spindle-shaped or their elongated cytoplasm contained occasional tonofilaments and irregularly shaped nuclei with single or double nucleoli. Rough endoplasmic reticulum was not abundant but dilated and the intercellular spaces of these cells were filled with collagen fibrils (Fig. 6). In one section an intranuclear and intracytoplasmic inclusion was seen (Fig. 8).

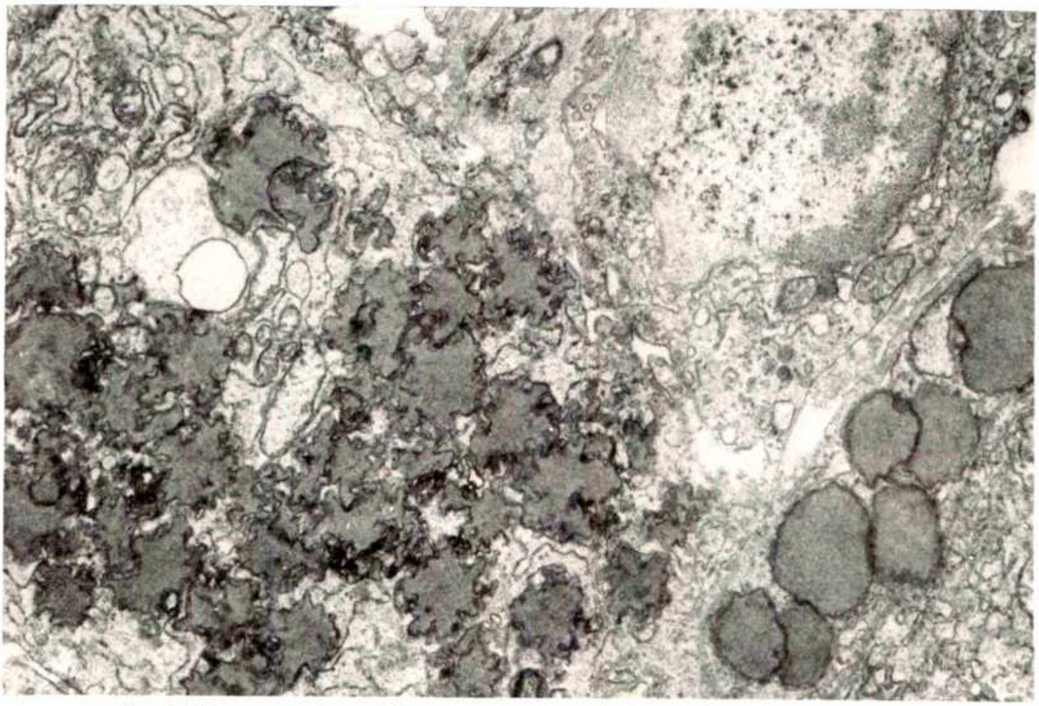

Fig. 7. A large number of fatty droplets in oval-shaped fibroblasts × 3500

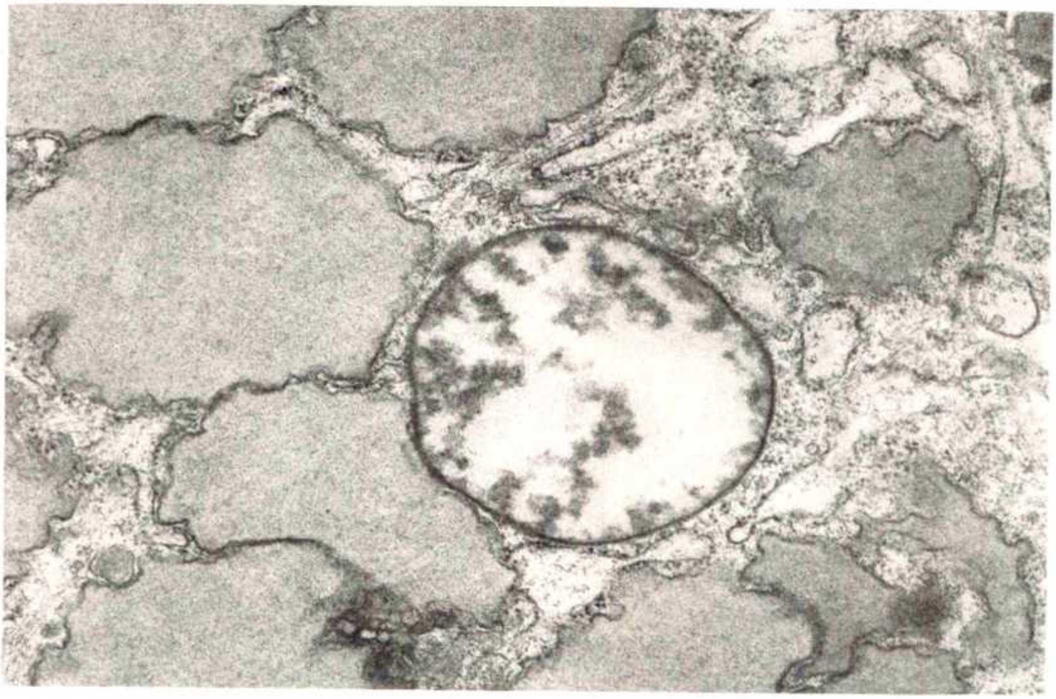

Fig. 8. An intracytoplasmic inclusion body in a fibroblast × 10 500

Round or oval-shaped histiocytic cells containing intracytoplasmic lysosomal bodies appeared to be scattered throughout the section but no inclusions were found (Fig. 6).

DISCUSSION

Because of the variety of histological features, plasma cell granuloma has been associated with many other granulomatous diseases of the lung, such as histiocytoma, xanthoma, xanthofibroma, mast cell granuloma or sclerosing haemangioma. In a discussion on whether a plasma cell granuloma is a neoplasm or a granuloma, Spencer (1968) classified plasma cell granuloma as a member of a group of rare pulmonary tumours of doubtful nature, but probably granulomatous. Bahadori and Liebow (1973) also considered plasma cell granulomas to be inflammatory and their close relationship to other inflammatory lesions has been described (McCully et al. 1973).

Morphologically, Bahadori and Liebow (1973) defined the plasma cell granuloma as a tumour which commonly contains plasma cells mixed with other inflammatory cells. Typically, this tumour is characterized by localized proliferations of mature plasma cells with Russell bodies. It is usually well separated from adjacent normal lung parenchyma but lacks a definite encapsulation. Apart from plasma cells, so called lipid laden cells or fatty cells, most of which were identified as fibroblasts in our case, are found abundantly. Histiocytic cells may also be present in this lesion.

Certain other tumours may be related to plasma cell granuloma. The term xanthoma is used when the major cellular component is a fat-filled cell (Grossman et al. 1973). The term mast cell granuloma is used when large numbers of mast cells are found. Furthermore, Wentworth et al. (1968) described a xanthomatous pseudotumour in which the cell components of the tumour were spindle cells, foamy cells and inflammatory cells.

Because these granulomas share similar features we think that they may have a common cause. We think that the pathological diagnosis should be decided according to the predominance of the cell type.

Bahadori and Liebow (1973) insist that sclerosing haemangioma should be distinguished from plasma cell granuloma, because sclerosing haemangioma is a neoplastic tumour originating from angioblastic tissue, probably endothelial cells. However, in our experience of a few cases of sclerosing haemangioma the cells seen under the electron microscope were all epithelial cells and histiocytes.

It is extremely important that plasma cell granuloma is distinguished from the true plasmacytoma in which neoplastic proliferations of plasma cells are characteristic (Jimenez and Tavassoli 1976; Mazumdar et al. 1969). Plasmacytoma usually consists of uniform sheets of malignant myeloma cells and invades the surrounding parenchymal tissue. Moreover, in a plasmacytoma inflammatory cells are fewer.

Ultrastructurally, most of the plasma cells in the plasma cell granuloma we describe were mature with well developed rough endoplasmic reticulum. Atypical cells and mitotic figures were not seen. In malignant plasma cell tumour (plasmacytoma), as Schweeres et al. (1976) described, the tumour cells show more atypical electron microscopic features, such as pleomorphism and active mitoses.

Fibroblasts seen in our case showed an unusual ultrastructural appearance: numerous fatty droplets were seen in the cytoplasm of spindle cells. It is not certain whether the fatty cells originate from fibroblasts or from another mesenchymal special cell (Arthur 1969). Large mononuclear cells which were identified as histiocytes were found in smaller numbers in the case presented here, although difficulties were encountered in distinguishing fibroblasts from histiocytes, as in the case reported by Wentworth et al. (1968).

McCully et al. (1973) pointed out that viral infection might be a possible cause of plasma cell granuloma. We observed intranuclear and intracytoplasmic inclusions in the fibroblasts, but failed to identify these inclusions as related to viral infection.

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THE BRONCHODILATOR EFFECTS OF CHLORPHENIRAMINE IN CHILDHOOD ASTHMA

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Summary

Significant improvement in lung function has been demonstrated following the inhalation of chlorpheniramine. The doses which were used caused local irritation and are probably unsuitable for routine clinical use. Nevertheless, we believe that antihistamines deserve further investigation in the treatment of childhood asthma.

INTRODUCTION

Although histamine is widely regarded as playing a central role in the genesis of bronchoconstriction in asthma (Schild et al. 1951), antihistamines have not found a place in the treatment of this condition and are generally considered to be inactive (*Lancet* 1955). Their failure to produce bronchodilation may be due to inadequate local concentrations of antihistamine or even to a histamine-releasing action (Hawkins 1955).

Popa (1977) showed that large intravenous doses of chlorpheniramine produce bronchodilation in adult asthmatics. This drug is an H_1-blocker with little atropinic or anti-serotonin activity (Tozzi et al. 1976). Apart from causing drowsiness, it is safe and free of side effects. As β_2-adrenergic stimulants may be very effectively administered as a nebulized solution with fewer side effects than equivalent oral or intravenous therapy, we conducted a pilot study to determine whether chlorpheniramine was an effective bronchodilator in childhood asthma when inhaled in this way.

Patients and Methods

Ten children, aged eight years seven months to 14 years two months (mean age 11 years), requiring regular treatment for chronic severe asthma, were studied. They had suffered from asthma for one to 12½ years (mean 6.3 years) with the onset of symptoms between the ages of six months and 13 years (mean 4.5 years). Heights ranged from 117 to 163 cm (mean 140.9 cm) and weights from 19.95 to 49.5 kg (mean 31.3 kg). Six children had a family history of atopy and the three children on whom skin tests had been performed showed positive reactions to multiple antigens. Seven children had required hospital admissions (range one to six) and eight had been treated with courses of oral steroids. No child was receiving oral steroids at the time of testing. Their routine medication included salbutamol by inhalation (ten), beclomethasone diproprionate (eight), sodium cromoglycate (two) and theophylline (one).

All children had previously undergone lung function testing and were accustomed to the procedures employed.

Patients were asked to stop routine medication at least 12 hours before testing. On arrival in the respiratory function laboratory they were questioned about their recent health and a clinical examination was performed. Base-line measurements of peak expiratory flow rate (PEFR) (best of three attempts using a Wright's peak flow meter), forced vital capacity (FVC) and forced expiratory volume in 0.75 seconds ($FEV_{0.75}$) (best of two satisfactory attempts using a Morgan water-filled spirometer) were recorded. The measurements were repeated after a 15-minute rest. The children then inhaled a solution of chlorpheniramine in sterile water using a commercially available face mask and nebulizer (Pari). Respiratory function tests were repeated 2, 5, 10, 15, 20, 30, 45, 60, 75, 90 and 120 minutes following inhalation. Finally, they inhaled 1 ml of nebulized 0.5% salbutamol respirator solution made up to 2 ml with water. Respiratory function tests were repeated 15 minutes later. The children were studied on three occasions (whenever possible on three consecutive days), when they were treated respectively with 2, 4 and 8 mg of chlorpheniramine maleate made up to 2 ml by dilution of the standard intravenous preparation with water. These doses were selected as less than 25% of the solution is inhaled and available for systemic absorption, making the maximum nebulized dose approximately equal to the usual oral dose. The spirometry readings were corrected to BTPS.

The project was approved by the local Ethical Committee and informed parental consent was obtained on all occasions.

RESULTS

There was considerable variation in the base-line measurements of lung function when calculated as a percentage of expected from height (Cogswell et al. 1975*a*, *b*). Initial PEFR and $FEV_{0.75}$ were within 25% of expected on 14 of the 30 and nine of the 30 assessments respectively.

The children tended to have more severe airways obstruction on the day they attended for the 4 mg dose (Figs 1, 2) but the differences between the base-line readings did not reach statistical significance. The inhalation of chlorpheniramine produced coughing on

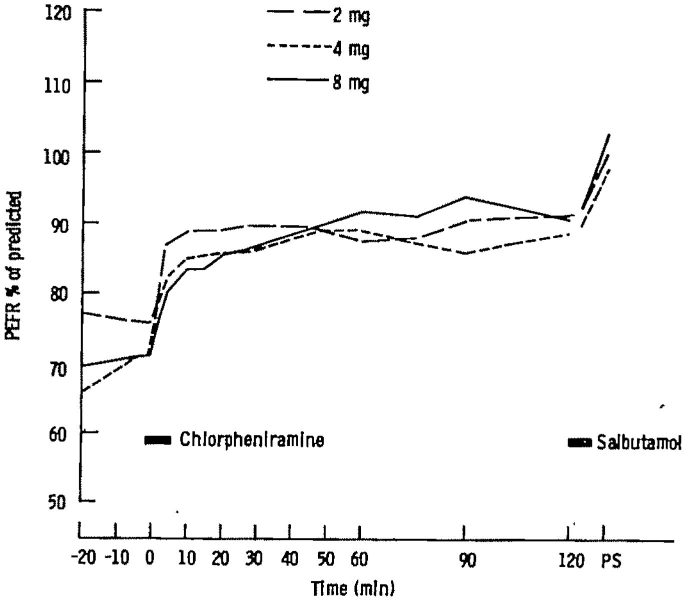

Fig. 1. Changes in PEFR after inhalation of solutions containing 2, 4 and 8 mg of chlorpheniramine and 5 mg of salbutamol in ten children with asthma

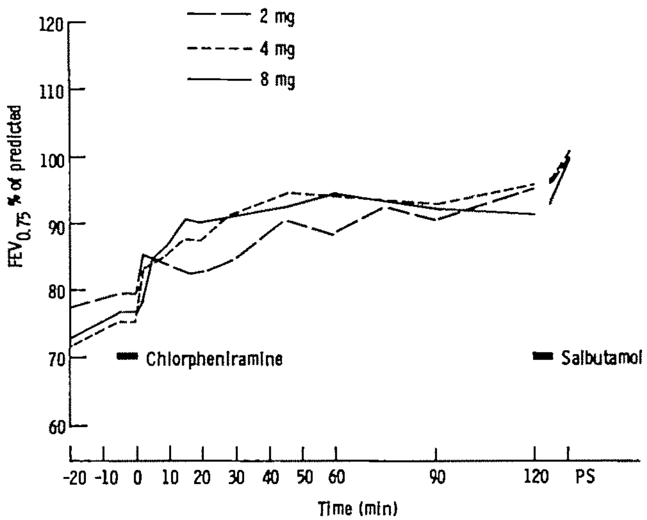

Fig. 2. Changes in $FEV_{0.75}$ after inhalation of solutions containing 2, 4 and 8 mg of chlorpheniramine and 5 mg of salbutamol in ten children with asthma

13 of the 30 occasions. This occurred at all doses and on three occasions was associated with a fall in either PEFR or $FEV_{0.75}$ of between 5 and 15% at two minutes. Three of the children coughed at all doses. However, all three treatment groups showed an improvement in PEFR and $FEV_{0.75}$ at two minutes which progressed over the next 30–45 minutes (Figs 1, 2). Further rises in PEFR and $FEV_{0.75}$ were seen after the inhalation of salbutamol at two hours, so that the group means all finished within 8.2% of the expected. When expressed as a percentage change from the initial reading, most post-treatment results were significantly better than the base-line (Tables I, II). Although

Table I. Mean percentage change in PEFR (±1 SD) from initial value

Time (min)	*Chlorpheniramine dose*		
	2 mg	4 mg	8 mg
2	7.3±15.3	15.1±22.6	11.5±20.2
5	19.0±22.4*	19.1±26.3*	17.7±22.1*
10	20.6±20.6*	22.5±22.8*	21.2±22.4*
15	21.7±24.0*	23.6±25.2*	21.2±21.4*
20	22.3±22.3 (9)*	25.5±25.2*	25.5±21.9†
30	23.0±26.7*	25.6±23.7*	27.9±27.7†
45	23.1±28.7*	30.2±29.7*	32.8±33.1*
60	27.8±33.1 (8)*	29.4±30.7*	36.5±33.7†
75	26.4±36.5 (5)	27.6±31.6*	36.0±35.2†
90	33.8±33.7 (6)	26.1±32.6*	40.2±33.5†
120	38.3±44.5 (4)	30.4±33.9*	34.2±28.8†
Post Sal	42.1±40.3	46.9±38.1	60.3±53.3

$\left.\begin{array}{l} {}^{*}P<0.5 \\ {}^{\dagger}P<0.01 \end{array}\right\}$ compared with initial, using Student's *t*-test.

Table II. Mean percentage change in FEV$_{0.75}$ (±1 SD) from initial value

Time (min)	Chlorpheniramine dose		
	2 mg	4 mg	8 mg
2	11.1±20.2	9.8±23.9	5.6±23.6
5	13.0±37.0	12.4±30.0	16.1±20.2*
10	10.4±35.2	13.5±26.9	18.0±14.7†
15	8.7±30.4	18.1±29.5	24.5±16.8†
20	9.9±35.8 (9)	17.3±30.8	25.5±22.4†
30	11.9±32.3	23.7±27.7*	28.3±25.2†
45	22.9±38.1	29.4±31.2*	30.6±30.0*
60	21.0±26.4 (8)*	29.8±33.6	32.8±24.9†
75	9.2±7.8 (5)	27.4±25.2†	33.0±33.1*
90	12.0±17.1 (6)	28.3±40.0	29.3±28.2†
120	14.5±17.7 (4)	33.6±38.8*	28.6±26.2†
Post Sal	38.9±29.9	44.4±47.5	48.9±46.3

* $P<0.05$ } compared with initial, using Student's *t*-test.
† $P<0.01$

Table III. Number of children with greater than 15% improvement in PEFR or FEV$_{0.75}$

Chlorpheniramine dose	Improvement in PEFR		Improvement in FEV$_{0.75}$	
	All	Init. <75%*	All	Init. <75%*
2 mg	5/10	4/6	5/10	5/8
4 mg	6/10	4/6	5/10	5/6
8 mg	6/10	4/4	7/10	5/7
Total	17/30	12/16	17/30	15/21

* Children whose initial results were less than 75% of the expected figure.

the improvement as measured by FEV$_{0.75}$ appeared to be dose related, only at 75 minutes did the difference between responses to the 8 mg and the 2 mg regimens reach statistical significance. The improvements in peak flow rate failed to show this trend. When the children were examined individually an improvement of at least 15% was seen on 17 occasions (Table III). Considering only those occasions when initial values were less than 75% of expected, a response was seen on 12 out of 16 occasions as determined by PEFR and 15 of 21 by FEV$_{0.75}$ (Table III). Only 50% of those children who failed to respond to chlorpheniramine showed an improvement of 15% or more when treated with salbutamol.

Discussion

Recent work by Nogrady et al. (1978), following that of Popa (1977), suggests that the place of antihistamines in the management of adult asthma needs to be re-examined. Both these groups have shown that antihistamines, if given in appropriate doses by appropriate routes, will lead to appreciable bronchodilation. We used chlorpheniramine because of Popa's encouraging findings and because it is a relatively pure antihistamine with few antiserotonin and anticholinergic effects. The nebulized route was selected as this provides a simple means of producing high concentration in the lung without the need for injection and with little systemic absorption.

This was a preliminary open trial attempting to determine whether chlorpheniramine was an effective bronchodilator when given by inhalation and to identify the most appropriate dose. The response to chlorpheniramine was often apparent within two minutes and reached a plateau by 30–45 minutes, rather earlier than the 60 minutes observed in adults using inhaled clemastine or intravenous chlorpheniramine (Popa 1977; Nogrady et al. 1978). As the response to the three dose regimens was broadly similar, we consider it unlikely that higher concentrations would produce further improvements. Nevertheless, most children improved further after the inhalation of salbutamol. This may be related to the different modes of action of the two drugs. The coughing which sometimes led to a slight fall in lung function makes the concentrations used in this trial unsuitable for general clinical use. It may be that smaller concentrations can be tolerated without loss in therapeutic response.

ACKNOWLEDGEMENTS

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THORACIC COMPLICATIONS OF AMOEBIC LIVER ABSCESS

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Summary

We report the cases of 170 patients with thoracic complications from amoebic hepatic abscess. The clinical, radiological and therapeutic features of the condition are discussed. Mortality is high, especially where poverty has already impaired health.

Introduction

Amoebiasis is of world-wide distribution (Bockus 1966) and in many tropical and subtropical countries, e.g. Mexico, it is endemic. In 1611 the death of Fray Garcia Guerra was apparently due to a large hepatic abscess which drained through the chest wall. Jimenez (1866) established the management of the problem. With modern anti-amoebic agents the prognosis of the intestinal and extraintestinal forms of the disease is good, except for some of the severe complications which still have a high mortality (Ortiz de Montellano & Topete 1960). The most common extraintestinal complication is amoebic hepatic abscess (Flores Barroeta et al. 1959), which in turn has severe thoracic complications. A study of these complications is presented here.

Material and Methods

The cases of patients with thoracic complications of amoebic hepatic abscess treated at this unit during the period 1968–73 were reviewed. There were 170 cases. The complications encountered were right pleural effusion (2%), rupture into the right pleura with empyema (32%), rupture into the left pleura with empyema (2%), rupture and drainage through the bronchi (42%), rupture into the pleura and drainage through the bronchi (21%) and rupture into the pericardium (2%).

The ages of the patients ranged from 14 to 81, with the highest incidence from 21 to 50 years of age. There were three times as many men as women. More than 75% of the patients were alcoholics: 70% drank *pulque*, a local fermented beverage made from the *maguey* cactus, and 30% drank other types of alcohol. About two-thirds were malnourished. In about 40% of cases there was diarrhoea of unidentified cause. Only in 2% was the parasite identified.

Results

The predominant symptoms recorded were right upper quadrant abdominal pain (63%), cough (89%), sputum production (82%), haemoptysis (65%), purulent sputum (34%), right lower chest pain (37%), dyspnoea (38%) and fever (84%).

The main radiographical findings were elevated right hemidiaphragm (91%), pleural effusion (50%), consolidation (39%), subdiaphragmatic fluid level (31%), enlarged pericardium (2%) and pneumopericardium (1%).

The cases were divided into three groups on the basis of the specific anti-amoebic medication used:

Group 1	Emetine hydrochloride and chloroquine
Group 2	Emetine hydrochloride, chloroquine and aminosidine sulphate and/or metronidazole
Group 3	Without emetine hydrochloride

Surgical procedures were carried out in 105 cases, as follows: closed chest drainage (39%), pleurocentesis (12%), decortication (7%), pulmonary resection of diseased lung parenchyma (3%) and pericardiotomy (2%).

Important sequelae encountered were pleural thickening (22%), bronchiectasis (15%) and pulmonary abscess (4%).

According to the clinical and radiographic evidence, good results were achieved in 59%, fair in 8%, poor in 3%, death in 19% and final result unknown in 11% of patients who failed to return for follow-up examinations.

Discussion

Thoracic complications of amoebic hepatic abscess are common where amoebiasis is endemic. They represent 5% of our hospital admissions (Rivero Serrano 1973). Complications occur in about one-fifth of those patients with amoebic liver abscess (Sepúlveda 1970). In order of frequency complications are rupture and drainage through the bronchi, rupture into and empyema of the right pleura, rupture with empyema and bronchial drainage, right pleural effusion without empyema and, uncommonly, pleural empyema and rupture to the pericardium. The highest incidence is in males between 20 and 50 years of age; malnutrition and alcoholism are frequently associated with the infection. Predominating respiratory symptoms are chest pain, productive cough with bloody or purulent sputum and dyspnoea. The latter is more common in patients with large effusions. The pleural effusion does not necessarily contain pus from the hepatic abscess, but may be due to severe irritation adjacent to it or secondary to a relatively small abscess (Rivero Serrano & Barraza 1963). The usual physical findings are tender hepatomegaly or tenderness on deep right upper abdominal pressure (Pande & Srivastana 1966; Hinshaw 1969), right pleural effusion, right diaphragmatic elevation and right lower lobe consolidation.

A routine chest radiograph in the posteroanterior and right lateral positions is, in our experience, the most useful diagnostic aid. The main findings are described above. In all our patients with elevated right diaphragm or right lower lobe opacities we introduced 400–800 ml of air as a pneumoperitoneum and repeated the radiographs in the upright position. If no air collected between the liver and diaphragm, owing to adhesions (Hinshaw 1969), we considered this pathognomonic of hepatic abscess, most likely amoebic (Rivero Serrano & Barraza 1963). Liver scintillography is also useful in diagnosis of the location, size and number of the abscesses.

For medical treatment of thoracic complications we used the drug of choice: emetine hydrochloride parenterally at a dose of 1 mg/kg daily for 10 days, up to a total of 600 mg. Electrocardiographic monitoring is essential because of the myocardial toxicity of the drug. Chloroquine phosphate is administered at the same time at a daily dose of 500 mg orally for three weeks. Other useful drugs include aminosidin sulphate, 15–20 mg/kg daily in three oral doses, and metronidazole, 40 mg/kg daily in three oral doses (Portes Borbolla et al. 1967).

Patients undergoing surgical procedures nonetheless require drug treatment of complications, particularly pleural or pericardial complications and their sequelae.

The mortality rate is still high (18%) in this series, which is higher than previous reports (Rivero Serrano & Barraza 1963; Medina & Vigueras 1966; Portes Borbolla et al. 1967; Valdez Ochoa et al. 1968; Rivero Serrano 1973). This leads us to believe that we are now seeing a more aggressive form of amoebiasis and to agree with Sepúlveda's (1970) concept of invasive amoebiasis. The poor general health of these patients, arising from poverty, makes the illness worse.

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SURGICAL REPAIR OF TRACHEOBRONCHIAL COMPRESSION BY TUBERCULOUS LYMPH NODES

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Summary

We describe a patient with a tuberculous lymph node pressing on the trachea and right lobe of the bronchus who was managed with resection of the node and Dacron patch closure of a defect in the tracheobronchial tree.

INTRODUCTION

Tuberculosis may lead to enlargement of the paratracheal and parabronchial lymph nodes and compression of the adjacent structures (node compression syndrome) (Watkins 1952; Mair 1969; Malatinsky & Sashegyi 1970). Such a case treated surgically by extirpation of the enlarged lymph node and repair of the residual tracheal defect by a Dacron patch is the subject of this paper.

Case Report

A three-year-old boy was referred to our hospital with fever, cough, and dyspnoea. Stridor and dyspnoea leading to cyanosis had been present for eight months. Lymph node biopsy of the neck had been carried out three months before, revealing tuberculosis. Antituberculosis drugs were not helpful. There was no family history of tuberculosis.

Physical examination showed a breathless restless child with diffuse wheezing and stridor. Sedimentation rate was 32 mm/hour. The peripheral blood showed lymphocytosis (36%). The PPD test was 10 mm positive. The chest radiograph showed a mass in the right hemithorax compressing the trachea and right main bronchus (Fig. 1).

Right thoracotomy was performed in August 1975. A mass 5 × 6 × 6 cm adherent to the trachea was found. The mass was punctured and pus was removed together with necrotic tissue material. It was thought that this was enlarged tuberculous lymph node. An air leak was observed from the trachea when the mass was removed. There was a defect on the tracheobronchial junction about 4 × 1.5 cm in size. The defect was closed with a Dacron patch with interrupted silk sutures. The patch was shaped to prevent airway obstruction (Fig. 2). Intact parietal pleura was sewn over the patch. The chest was closed in the usual manner.

Pathological examination of the specimen confirmed tuberculosis. Antituberculosis treatment was started. A control bronchogram taken 40 days after the operation showed that there was no leak and the airways were patent (Fig. 3). The patient was readmitted to the paediatric unit in February 1976 with fever and tachycardia. On the seventeenth day of admission he died in a hepatic coma of unknown cause.

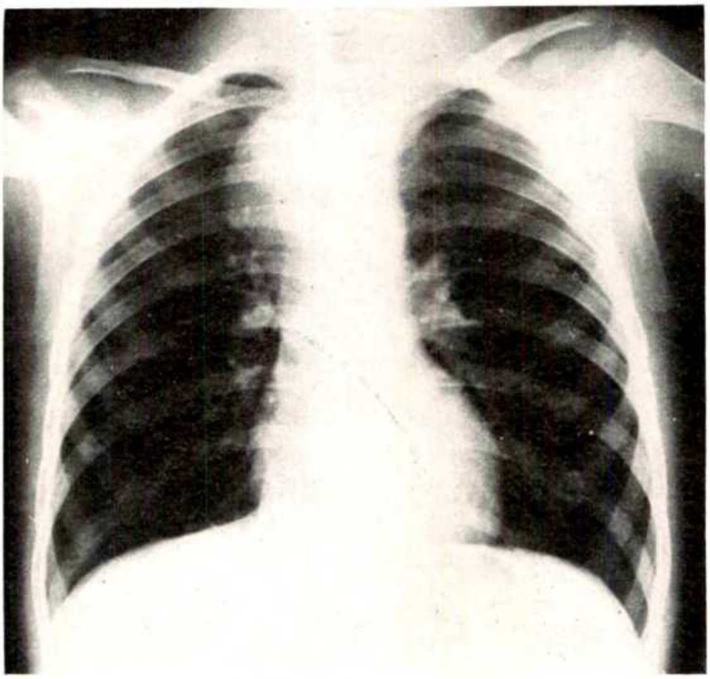

Fig. 1. Preoperative radiograph

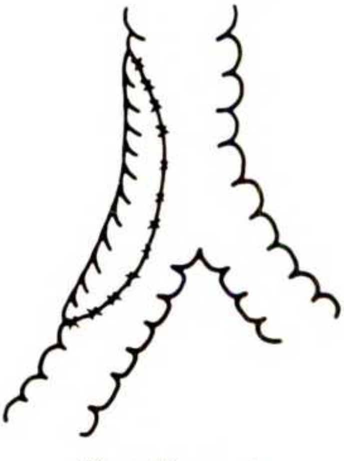

Fig. 2. The patch

DISCUSSION

Tuberculous lymph nodes in children may cause pressure or traction on the adjacent organs (node compression syndrome) which can lead to bronchiectatic changes in the lungs (Watkins 1952; Grillo 1965; Mair 1969; Malatinsky & Sashegyi 1970). Compres-

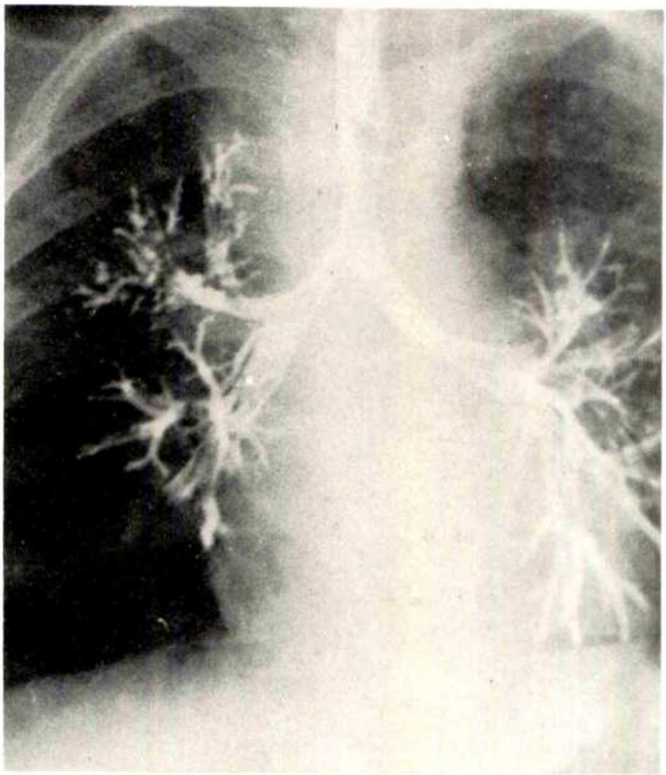

Fig. 3. Postoperative bronchogram showing no leak

sion of the trachea by these lymph nodes as observed in our case is very rare (Grillo 1965; Gerbeaux 1970; Linchtenaur et al. 1970; Malatinsky & Sashegy 1970). Caseous material from the lymph nodes may be spread in the tracheobronchial tree as the result of perforation and obstruct the airways, leading to sudden death. This complication is very rare, one case having been reported in 4041 patients with tuberculosis (Gerbeaux 1970). This complication might have developed in our patient if the operation had not been carried out.

Pericardium, dura mater and skin grafts have been used in the closure of the defects on the tracheobronchial walls. Teflon and Dacron are now more commonly used (Paulson 1951; Burke 1962; Mair 1969; Linchtenaur et al. 1970).

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PULMONARY TELANGIECTASIA

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Summary

Two patients with pulmonary telangiectasia are described. One of these is by far the oldest yet reported. The diagnosis and prognosis of this condition are discussed.

INTRODUCTION

Pulmonary telangiectasia is a rare, diffuse anomaly of the pulmonary vasculature in which there are innumerable anastomoses between peripheral branches of the pulmonary arteries and veins. It is related to hereditary haemorrhagic telangiectasia (Osler–Rendu–Weber syndrome), some patients with pulmonary telangiectasia having skin and mucous membrane vascular lesions. More commonly patients with hereditary telangiectasia may have large discrete pulmonary arteriovenous fistulae. Telangiectasia may be a developmental abnormality of vessels arising from a common capillary plexus or may be caused by an enlargement of pre-existing minute communications between pulmonary arterioles and venules (Tobin 1966). Eighteen cases of pulmonary telangiectasia have recently been reviewed by Currarino et al. (1976). One further case described by Genovesi et al. (1976) makes a total of 19 reported cases in the world literature before the cases described here. All previous cases have been children or young adults, the oldest being 30 years of age. This paper reports the cases of two patients, one a child of 10 years, the other a woman of 58 years. The diagnosis and prognosis of this condition are discussed.

Case Reports

Case 1

A 58-year-old married woman was first seen to be cyanosed at the age of 14 years. Despite the persistence of cyanosis she led an unrestricted life and had two normal pregnancies at the ages of 28 and 30 years. For the last three years she had noticed dyspnoea on moderate exertion. There was no family history of cyanosis, clubbing or haemorrhage. She looked well but had marked central cyanosis and finger-clubbing. There was no abnormality of the skin or nasal, oral and rectal mucosa. Examination of the cardiovascular and respiratory systems was normal. The haemoglobin concentration was 18 g/dl and the haematocrit 56%. The red cell volume was 54 ml/kg (normal range 20–30 ml/kg). There were no abnormal haemoglobin pigments. The electrocardiograph was normal. Chest radiographs revealed a slightly enlarged heart and minimal enlargement of the main pulmonary arteries. There were multiple nodular shadows of different size throughout both lungs predominantly in the lower zones (Fig. 1). The radiographic appearance had not changed over a period of 12 years. Ventilatory tests showed no evidence of airway obstruction but there was some reduction in lung volumes by helium dilution and a marked reduction in carbon monoxide transfer factor (Table I). Right heart catheterization revealed normal pressures. Intracardiac shunts were excluded by oxygen saturation measurements and dye curves. There was arterial desaturation, the aortic P_{O_2} being 6.1 kPa (46 mmHg), haemoglobin saturation 76%. Full oxygenation was not

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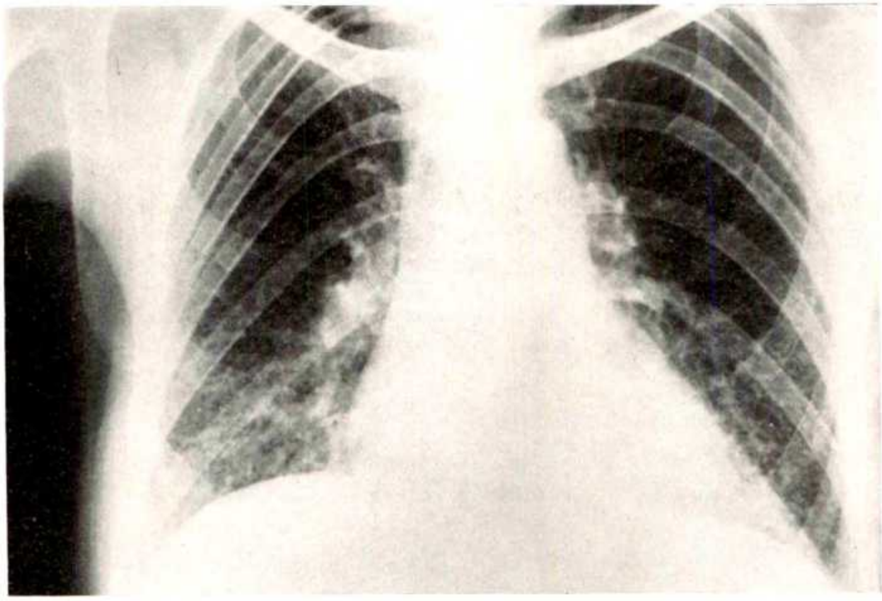

Fig. 1. Case 1. Chest radiograph showing diffuse nodular shadowing particularly in the lower zones

Table I. Lung function tests

	Case 1			*Case 2*		
	Pred.	Obs.	% pred.	Pred.	Obs.	% pred.
Peak expiratory flow rate (litres/min)	357	360	101	250	180	72
Forced expiratory volume in 1 second (litres)	2.1	1.7	81	1.7	1.35	79
Vital capacity (litres)	2.5	2.0	80	1.9	1.7	90
Forced expiratory volume/vital capacity	82	85	—	89	73	—
Residual volume (litres)	1.7	1.2	71	0.5	0.7	140
Functional residual capacity (litres)	3.4	1.7	50	1.0	1.3	130
Total lung capacity (litres)	4.3	3.2	74	2.4	2.5	104
Residual volume/total lung capacity	38	38	—	23	31	—
Transfer factor for carbon monoxide (mmol/min/kPa) (ml/min/Torr)	7.37 (22)	3.68 (11)	50	5.36 (16)	2.61 (78)	49

achieved after breathing 100% oxygen through a non-return valve for 15 minutes, the P_{O_2} then being 10.5 kPa (79 mmHg), saturation 97%. Pulmonary angiography (Fig. 2) showed enlarged main pulmonary arteries with tortuosity of the distal arteries. There was filling of multiple abnormal vessels throughout both lungs predominantly in the lower zones. There was also early filling of pulmonary veins. These appearances were taken to confirm the diagnosis of pulmonary telangiectasia.

Case 2

A 10-year-old girl exhibited cyanosis and complained of dyspnoea on moderate exercise. In 1974

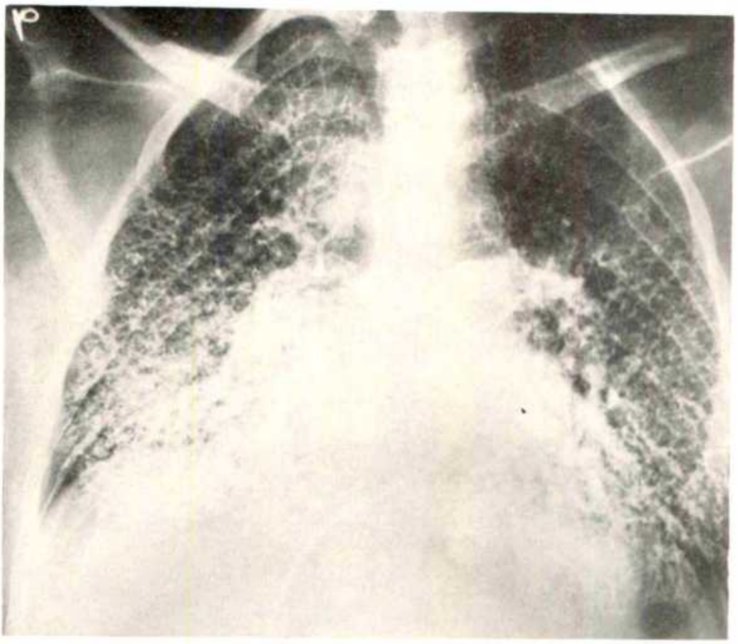

Fig. 2. Case 1. Pulmonary angiogram (capillary phase) showing filling of multiple abnormal vessels

she began to suffer from recurrent epistaxes which were treated by cauterization of the blood vessels in one nostril in 1975. At this time she was found to have an iron-deficiency anaemia and hepatomegaly. Cyanosis was noted when the anaemia responded to iron. She was an active child who, despite her dyspnoea, was able to swim and play with her friends, but did not take part in physical education at school. She had three fit siblings and there was no history of cardiac, pulmonary or bleeding disorders in her family. There had been a budgerigar at her home for one year but her symptoms began before this time. Her height was on the fiftieth percentile and weight on the seventy-fifth. There was obvious central cyanosis, early digital clubbing and two small facial telangiectases. No telangiectasia was seen in the mouth or nasal mucosa. The pulse rate was 110 and regular, blood pressure was 80/60 mmHg. There was mild right ventricular hypertrophy but no bruits arising from the heart or lungs were heard. Expansion of the chest was normal and no crackles or wheezes were heard. There was moderate hepatomegaly but the spleen was not palpable. Haemoglobin was 10 g/dl, red blood cell count 5.2×10^{12}/litre, white cell count 10.2×10^{9}/litre. The blood film showed hypochromia and microcytosis. β and γ globulins were increased, alkaline phosphatase and aspartate transaminase were twice normal and antimitochondrial antibody and rheumatoid factor were found in the serum. Needle liver biopsy was normal. An electrocardiograph was normal. Chest radiographs showed minimal, but definite, bilateral diffuse 2 mm nodularity (Fig. 3). Spirometry revealed mild airways obstruction but lung volumes, measured by helium dilution were normal. The carbon monoxide transfer factor was reduced (Table I). Cardiac catheterization revealed a slight increase in pulmonary artery and right ventricular pressures but no intracardiac shunt was demonstrated. The three pulmonary veins were sampled and showed oxygen saturations of 71–85%, $P\text{O}_2$ of 6.3–6.8 kPa (47–51 mmHg). On breathing 100% oxygen the saturations increased to 99%, $P\text{O}_2$ to 21.7 kPa (163 mmHg). The pulmonary angiogram (Fig. 4) showed mild tortuosity of the pulmonary arteries in the lower zones and a diffuse abnormal vascularity in the late arterial phase, the normally inconspicuous capillary phase and the early venous phase. There was early filling of pulmonary veins. Following the catheterization the patient had a small haematemesis which was presumed to be due to bleeding from gastrointestinal telangiectasia.

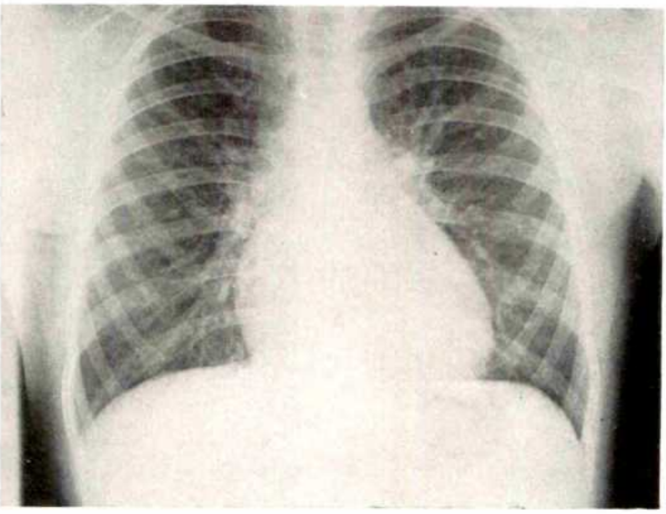

Fig. 3. Case 2. Chest radiograph showing minimal nodularity

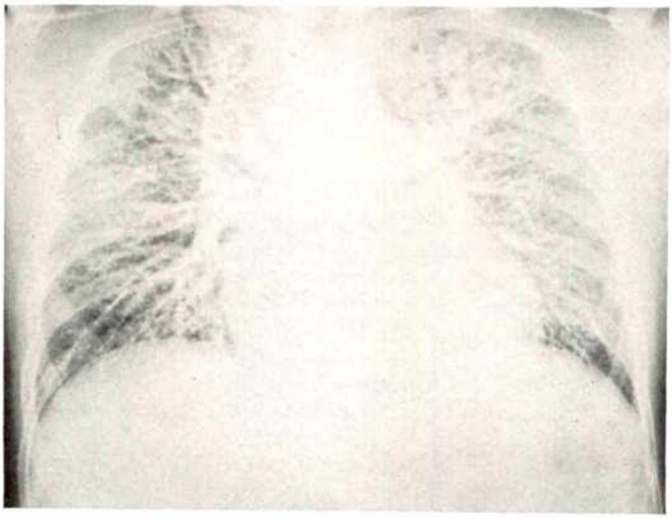

Fig. 4. Case 2. Pulmonary angiogram showing a diffuse abnormal vascularity in the normally inconspicuous capillary phase

DISCUSSION

Both of our patients were originally misdiagnosed as suffering from pulmonary fibrosis. There are several points to note in making the differentiation. The cyanosis was out of proportion to the dyspnoea for diffuse interestitial fibrosis. The posture-dependent late inspiratory crackles of fibrosis were not present. The carbon monoxide transfer factor is reduced in pulmonary telangiectasia due to a reduction in the pulmonary capillary volume, but lung volumes are not usually reduced. Though right to left intracardiac shunts are usually obvious on examination Eisenmenger's syndrome has been incorrectly diagnosed in this condition. If pulmonary parenchymal and cardiac abnormalities are excluded there must be an extracardiac shunt, either a large arteriovenous fistula or many small ones. In some cases of pulmonary telangiectasia the chest radiograph has been recorded as normal, but usually there are small nodular shadows throughout the lung fields.

Our first case is of interest in that she is by far the oldest patient with pulmonary telangiectasia to be described, the duration of her signs being at least 44 years. All previous cases have been children or young adults, the oldest to date being 30 years (Genovesi et al. 1976). The prognosis of this condition has generally been considered poor but it now seems that this is not always the case and pulmonary telangiectasia must be considered in an older age group. Deterioration appears to be related to a progression in the size and number of telangiectasia. For some unknown reason this progression appears to have halted in our first case. The second case appeared to have an associated hepatic disturbance. Hepatic haemangiomata have been found in some cases and others have had abnormal liver function (Sanders & Martt 1962). Abnormalities of pulmonary circulation with arteriovenous anastomoses are well recognized in cirrhosis (Karlish et al. 1967) but in our case this condition was excluded by a normal liver biopsy.

Once the diagnosis is suspected it is best confirmed by pulmonary angiography. The findings in other reports have been as described in our cases. Dye curves do not show the two peaks of a shunt but there is rapid appearance of dye showing an increased transit time. In most cases reported the breathing of 100% oxygen does not correct the haemoglobin desaturation. In our second case the saturation rose to 99%. It appears that at high oxygen tensions the abnormal vessels can participate in gas exchange. Therefore this method of estimating shunts may underestimate their size. Two groups of workers have described the use of radioisotope labelled macro-aggregated albumin to assess the size of the shunt (Currarino et al. 1976; Genovesi et al. 1976) Anatomical studies have been described in nine patients, six at necropsy and four by lung biopsies. The changes have been variously described as dilatation of precapillary vessels resembling telangiectasia, disseminated foci of angiomatous proliferations and scattered vascular plexuses, the larger of them resembling cavernous haemangiomata. Lung biopsies, however, are clearly inadvisable in the diagnosis of this condition.

ACKNOWLEDGEMENT

We would like to thank Dr M. R. Stephens and Dr B. M. Ansari for allowing us to report their cases, Dr M. Ruttley and Dr L. G. Davies for their technical assistance and Dr A. Seaton for his advice.

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CHRONIC PLEURISY IN SYSTEMIC LUPUS ERYTHEMATOSUS TREATED WITH PLEURECTOMY

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Summary

Pleural involvement, clinically and radiologically, is common in systemic lupus erythematosus but it is usually transient and rarely presents a management problem. In the two cases described here unremitting pleural pain was the dominant symptom. After failure of conservative treatment pleurectomy was performed in both cases with symptomatic relief.

Case Reports

Case 1

A 28-year-old woman presented in 1956 with Raynaud's phenomenon severe enough to cause ulceration of the finger pulps. In 1958 she complained of widespread arthralgic pains and pleuritic pain in the interscapular region. An erythematous rash was noted in butterfly distribution. Her chest radiograph was normal and no LE cells were detected. Prednisolone was started and with two short breaks has been continued at an average daily dose of 10–15 mg.

She remained reasonably well until 1966 when she was admitted because of arthritis of the wrists and hands. LE cells were demonstrated on three occasions. In 1969 she had a further flare-up of the arthritis and Raynaud's phenomenon. Cyclophosphamide was added and was continued for one year with some apparent benefit.

In 1971 she developed breathlessness and a constant ache in the left chest which lasted several months. Chest pain recurred in 1973 and was at times pleuritic although no rub was heard. The chest radiograph now showed pleural thickening at the left base. Cyclophosphamide was re-introduced for six months without effect. Throughout the next two years she complained of recurrent episodes of bilateral pleural pain. LE cells were again found and the antinuclear factor test was strongly positive. In 1974 she had an episode of acute pericarditis.

By 1976 she had almost constant pleuritic pain at both costal margins, more severe on the right. She was also breathless on slight exertion. Lung function tests showed a mild restrictive pattern of ventilation. Transfer factor was reduced to 14.2 ml/mmHg/min (predicted 21.9). As her chest pains were by then so disabling, a right pleurectomy was performed in March 1976 (Mr Gordon Jack). At operation the lung was found to be extensively stuck to the chest wall and diaphragm. The parietal pleural was excised.

After surgery she was free of pain on the right but continued to have left-sided chest pain. In view of the symptomatic success of the first operation a left pleurectomy was performed in November 1976. Since then she has remained almost completely free of chest pain. Currently her major problem is low back pain due to corticosteroid-induced osteoporotic vertebral collapse.

Histological examination of the pleura from the right chest showed a mild diffuse chronic inflammatory cell infiltrate throughout. Two nodular lesions, visible with the naked eye, microscopically contained arteries which showed severe fibrinoid necrosis. There was a dense perivascular infiltrate of polymorphs, lymphocytes and plasma cells which did not involve the vessel walls (Fig. 1). The pleura from the left side showed similar changes but no arteritis.

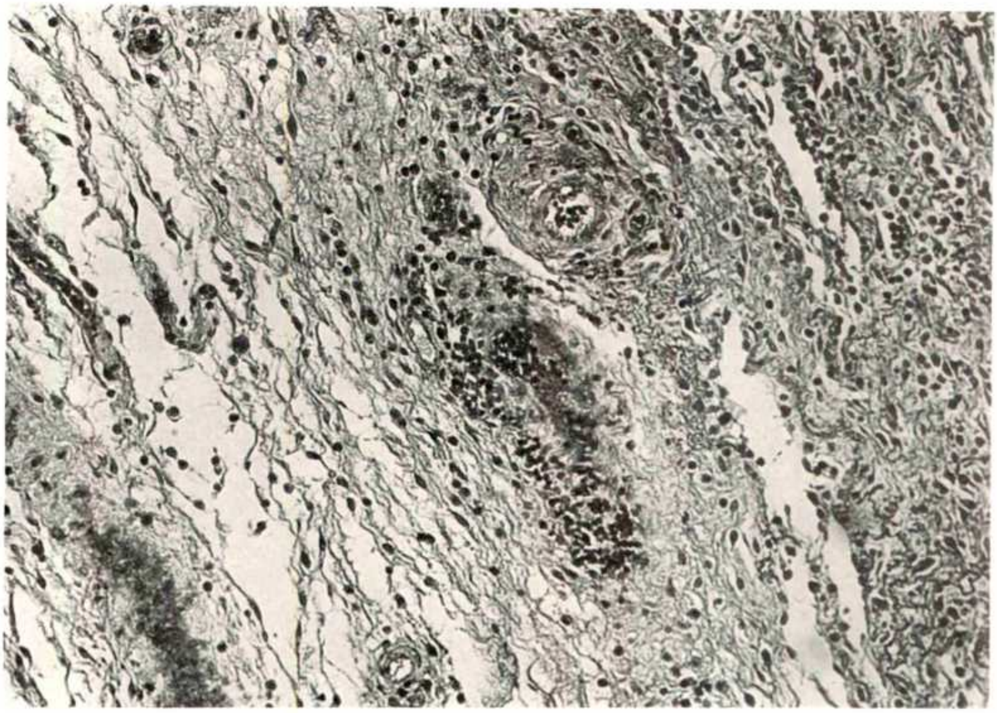

Fig. 1. Pleura from Case 1 showing generalized congestion and inflammatory cell infiltration. An artery at the centre of the field shows fibrinoid necrosis of its wall. × 105

Case 2

A 30-year-old woman presented in 1956 with fever and right-sided pleuritic pain. The chest radiograph showed a moderate sized right pleural effusion. The effusion was aspirated but no details of it were recorded. She suffered from a further episode of left pleuritic pain in 1962 and her chest radiograph showed a small effusion on that side. LE cells were not detected. In 1963 she again complained of persistent left pleuritic pain, severe enough to require pethidine. By 1964 her symptoms were still present and an exploratory left thoracotomy was carried out (Mr Gordon Jack). The pleural space over the lower two thirds of the lung was obliterated and pleurectomy was carried out. Pleural histology showed thickening by fibrosis. The tissue was vascular and was infiltrated by eosinophils, plasma cells and lymphocytes especially in the perivascular areas. There was, however, no evidence of arteritis.

After operation she remained generally well and free from pleurisy until 1966, when she developed widespread myalgic pains and generalized lymphadenopathy. The antinuclear factor test was positive and LE cells were demonstrated although subsequent tests were negative. Serum globulin levels persistently exceeded 40 g/litre.

In 1970 thyrotoxicosis, diagnosed at another hospital, was treated with radioactive iodine. Hypothyroidism occurred one year later and has been treated with replacement therapy.

The myalgic pains which began in 1966 have persisted and she has developed mild Raynaud's phenomenon. There has, however, been no recurrence of pleurisy or evidence of other system involvement. She has never received any specific drug therapy apart from chloroquine for one year in 1967. The patient has always refused corticosteroid therapy.

Discussion

The diagnosis in Case 1 is clearly validated by laboratory investigations, and, although

Case 2 rarely showed positive LE cells and antinuclear factor, taken with the features of pleuritis, Raynaud's phenomenon, myalgia and hyperglobulinaemia, these are felt to confirm systemic lupus erythematosus (Harvey 1960).

Pleural involvement is common in systemic lupus erythematosus, occurring radiologically in more than 30% of cases in several series (Garland & Sisson 1954; Moersch et al. 1956) and all cases in the series of Gould and Daves (1955). The main findings are pleural thickening and a small pleural effusion.

Pleuritic pain similarly occurs in about 50% of cases (Harvey et al. 1954; Dubois & Tuffanelli 1964) but a review of the literature did not yield reports of pleural pain as a chronic problem. Indeed Harvey et al. (1954) noted its duration generally as a few days, although sometimes recurrent.

Our reports suggest that occasional patients may have unremitting pain, not controlled by the usual methods. Pleurectomy appears to have been helpful in our cases, and should be considered in this situation. Our two patients felt surgery worth while.

ACKNOWLEDGEMENTS

We thank Dr L. Doyle for permission to publish these cases and Dr K. V. Lodge for help with the histology.

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Short Communication

ALPHA-ADRENERGIC BLOCKADE IN SEVERE ASTHMA

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Summary

Thirty-nine chronic asthmatics requiring steroids showed no response to the alpha-blocking drug indoramin during a double-blind trial.

INTRODUCTION

The hyperactivity of bronchial smooth muscle in asthma has been attributed by Szentivanyi (1968) to relative ineffectiveness of the bronchial beta-adrenergic receptors allowing unopposed bronchoconstrictor alpha activity. Standard treatment for asthma is usually aimed at stimulating the beta receptor, but more recently alpha-blockade has shown some promise (Campbell & Dyson 1977) raising the possibility that bronchospasm which persists in spite of treatment is at least in part due to unopposed alpha activity (Melville & Iravani 1974).

A clinical trial was set up to determine the effect of the long-acting alpha-blocking drug indoramin in chronic reversible asthmatics who had persistent symptoms in spite of treatment with beta stimulants and corticosteroids (oral, inhaled or both).

Patients and Methods

Forty-two patients who satisfied the following criteria were selected from the routine chest clinic:

1. Informed consent given.
2. Age 18–70 years.
3. Persistent wheeze every day for at least six months.
4. Continuing need for beta stimulants and corticosteroids.
5. Normal chest X-ray.
6. No evidence of other disease or pregnancy.
7. At least partly reversible airways obstruction, judged by at least two of the following criteria:
   (*a*) Documented evidence of 20% or more increase in FEV after treatment in the past.
   (*b*) 20% or more increase in FEV two minutes after two puffs of a Salbutamol inhaler.
   (*c*) History of variable dyspnoea and wheeze.

For the first four weeks all patients took one placebo tablet three times a day, in order to familiarize themselves with recording techniques. This part of the study was single blind. Patients then entered a double-blind crossover trial, being randomly allocated either indoramin (three 10 mg tablets three times a day) (group A) or the same number of identical placebo tablets (group B). After two weeks the dose was increased to four tablets three times a day if there was no improvement, or reduced to two three times a day if side effects occurred. After four weeks the groups crossed over and the procedure was repeated. Patients continued on unchanged doses of beta-stimulant aerosols and steroids but bronchodilator tablets were stopped at the beginning of the run-in period.

Assessment of progress was made by the following means:

1. Recording the best of three peak flow readings three times a day.
2. Recording the number of inhalations of beta stimulant aerosol.
3. A daily record of breathlessness by marking a line diagram.
4. Fortnightly recordings of FEV_1 and FVC.

RESULTS

Three patients were withdrawn during the placebo run-in period: two were worried about continuing the trial and one developed ulcerative colitis. Thirty-nine patients completed the trial. The mean peak flow of group A was 261 litres/minute while receiving indoramin and 259 litres/minute while receiving placebo. The corresponding means of peak flow for group B were 245 litres/minute and 241 litres/minute. Analysis of mean value week by week during the treatment period showed no improvement on higher doses of indoramin.

The frequency of use of beta stimulant inhaler was unchanged.

Symptoms recorded on line diagrams showed no difference between periods of active and placebo treatment.

Fortnightly figures for FEV_1 before and after inhalation of salbutamol showed no advantage of indoramin over placebo and no evidence of greater reversibility on indoramin.

The only side effect occurring in excess in the indoramin group was drowsiness, noticed by eleven patients.

Two patients, both in group B, became very wheezy after finishing the trial and responded to further treatment with indoramin. One of these continued treatment for nine months and then stopped the drug apparently without any worsening of dyspnoea. The other, aged 67, had a stroke which is not thought to be related to the treatment.

DISCUSSION

None of the observations show any superiority of indoramin over placebo, suggesting that, at least in the type of asthmatic we studied, alpha-blockade is not a useful advance in treatment and that unopposed alpha-stimulation is not a factor causing the irreversible element of airways obstruction.

ACKNOWLEDGEMENTS

I would like to thank John Wyeth (U.K.) for supplies of tablets and peak flow gauges, and Peter Johnson for the statistical analysis.

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Short Communication

PLEURAL THICKENING—OXPRENOLOL EXONERATED

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The recently reported patient with progressive pleural thickening during oxprenolol therapy (Page 1979) has subsequently been found at thoracotomy to have a malignant mesothelioma and not benign fibrous thickening of the pleura. While this development happily exonerates oxprenolol it highlights the difficulty in diagnosing this tumour.

As described in the previous report the subject concerned developed progressive pleural thickening in 1977. In March 1978 a closed pleural biopsy revealed a thickened pleura composed of dense fibrous tissue with areas of hyperplastic mesothelial cells but no evidence of malignancy. In the apparent absence of a malignant cause or of any other cause of the pleural thickening a possible association with oxprenolol therapy was suspected in view of the recent reports of practolol-induced pleural thickening (Dyer & Varley 1975; Fleming & Hickling 1975; Marshall et al. 1977). Over the past few months the development of dyspnoea prompted further investigation and small quantities of serous pleural fluid were aspirated in January and March 1979, both of which showed no cytological evidence of malignancy. In April 1979 a thoracotomy was performed with the object of decortication to relieve increasing dyspnoea. At operation the pleura had the appearances of a malignant tumour which histologically proved to be a malignant mesothelioma.

The failure to diagnose this tumour by closed pleural biopsy or by cytological examination of pleural fluid is in accord with the experience of others (Whitwell & Rawcliffe 1971; Elmes & Simpson 1976; Taryle et al. 1976) and is confirmed by an analysis of the ten cases of malignant mesothelioma diagnosed at the Regional Cardiothoracic Centre, Papworth, over the last ten years, in which closed pleural biopsies were performed. In only four cases was the diagnosis of mesothelioma made on the basis of the first biopsy and in four others the initial biopsy showed no evidence of malignancy. In these four cases and in two others with an initial biopsy diagnosis of adenocarcinoma, the correct diagnosis was made with a second biopsy (three cases), a third biopsy (one case) and in two cases at thoracotomy after repeated closed biopsies.

This experience accords with that of others, that the diagnosis of malignant mesothelioma cannot be discounted on the basis of a single closed pleural biopsy. If histological proof of diagnosis is thought to be necessary, repeated closed biopsies or an open biopsy may be required.

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BOOK REVIEWS

Major Problems in Clinical Surgery, XXI. Respiratory Distress Syndrome of Shock and Trauma

F. Williams Blaisdell and Frank R. Lewis

Philadelphia: Saunders. 1977. Pp. xii+237. Price £12.50

Professor Blaisdell is well known for his work on the role of thromboembolism in the genesis of pulmonary complications after major trauma. It is not surprising therefore that the best chapters in this book are those devoted to pathology and pathogenesis; they provide an excellent critical account of a difficult subject, although the novice would do well to heed the authors' clearly-stated apology for personal bias towards the particular importance of thromboembolism.

The remaining chapters are less stimulating and contain a mixture of basic physiology and clinical practice, varying in depth of discussion from considerable detail to bare outline. A more serious criticism is the lack of definition. It is stated that the respiratory distress syndrome can be defined 'relatively precisely' (!) once other causes of respiratory failure have been eliminated. This statement is not followed by any criteria, but 11 references are quoted, only one of which is more recent than 1973. Similarly, the sections on therapy and outcome cover respiratory impairment in general, and while it must be accepted that respiratory insufficiency after surgery or trauma is usually multifactorial in origin, more distinction between the relative importance of different factors would be welcome.

Those with a broadly-based interest in the whole spectrum of the adult respiratory distress syndrome may be surprised to see that the list of associated conditions includes carcinomatosis and peripheral vascular disease, but not acute pancreatitis, viral pneumonia or inhaled irritants. The purist, too, will resent the occasions when changes in compliance are quoted in the wrong direction. In general, however, errors are few, production is good and the price is not unduly alarming. Surgeons with a particular interest in the pulmonary complications of shock and trauma will want to read the chapters which reflect the authors' special interests and expertise; they will find little with which to disagree in the remainder of the text and little which is likely to change their current practice.

M. BRANTHWAITE

Diagnosis of Diseases of the Chest, Vol. I

Robert G. Fraser and J. A. Peter Paré

Philadelphia: Saunders. 1977. Second edition. Pp. xvi+726. Price $20.00

This is the first volume of the second edition of a well-known, respected text, written by two radiologists, but encompassing a wide range of chest medicine. In the seven years since the first edition the vast amount of new knowledge has led to a doubling of the number of volumes from two to four. This logarithmic increase raises the question of what the next seven years has in store.

Perusal of this volume confirms the known fact that this is a textbook of major importance to virtually anyone interested in the respiratory field. Thus radiology is only one facet of its approach to chest disease and the physician, physiologist, pathologist and others will all find much of interest. It includes descriptions of the normal chest, methods and techniques of investigation, clinical features and roentgenologic (would that Roentgen were simply called X) signs of chest disease in general, with congenital diseases. The breadth of the work is immediately apparent in Chapter 1, which includes excellent reviews of anatomy, physiology, host defence and metabolic functions of the lung, to mention but a few. The succeeding five chapters are similar in detail. Throughout the X-ray plates are excellent. Additionally the number of references (nearly 2000) means that one can virtually guarantee finding something new on any given topic.

From the foregoing any trace of fault may be inapparent. Nevertheless there are some. The size is somewhat awesome: 656 pages of text plus 70 of references and index. The style is verbose, to say the least, and cluttered with that guttural tongue-twister, roentgenogram; the substitution of X-ray would substantially shorten the book. Although there may be few other books encompassing so many different facets, nevertheless there are other specialized texts of physiology which give more lucid accounts. One questions whether too much detail has been included, adding to the book's considerable length. There are some trivial points of note: the use of grains, now long extinct elsewhere, evokes memories if little else. The adventitial sounds of the lungs, now crackles and wheezes in the modern idiom, are slightly dated, as are their described origins. Some terms, such as cicatrization atelectasis, are uncommon to the UK.

In conclusion, any criticisms are small compared with the value of this book as a general and X-ray text. Nevertheless one fears that the authors' comments in their preface to the second edition—that it becomes a reference book, albeit one that is indispensable to any doctor interested in the chest—may be realized by virtue of its size and number of volumes.

S. W. CLARKE

Respiratory Care: A Guide to Clinical Practice

George G. Burton, Glen N. Gee and John E. Hodgkin

Philadelphia: Lippincott (Oxford: Blackwell Scientific). 1977. Pp. xx + 1062. Price £36.00

Although large, this is a splendid book for those interested in basic respiratory care. It is well written, sentences being short and to the point, but with 'chatty' interjections, interesting derivations of technical words and historical aspects, and therefore easily read.

Once again this is a book on respiratory care written and produced in America, where the team dealing with the respiratory patient consists of different members from that in the UK and elsewhere. We have as yet no such category as the respiratory therapist. The first section of the book therefore—Respiratory Care Service and Education in the Modern Hospital—cannot be applied in its entirety to situations outside the USA. It does, however, give an interesting picture of the organization of an American respiratory unit, including the duties and responsibilities of the medical director of such a unit and education of personnel and budgeting funds and also of American legal aspects of respiratory care.

The second section—Rational Scientific Basis for Respiratory Therapy—has 19 divisions by different contributors. This book sets out to be completely clinical in its approach and this is shown in all areas even the anatomical section where differences in anatomical structure are related to disease performance, i.e. 'interlobar septa being less clearly defined in central portion of lung, being a possible explanation of the more rapid spread of alveolar lesions such as bronchopneumonia', and this maintains the interest of the clinical reader through most sections of the book.

This book obviously does not go into the physiological details found in books of respiratory physiology, but all the necessary facts for the intelligent understanding and treatment of respiratory problems are distilled and concisely presented, always with a clinical approach. Because this book is directed at a wide range of staff, it is at times very basic in approach and goes into some practical procedures in great detail, for instance the performance of an arterial puncture. This is also shown in a very basic physical examination description, with a useful table of physical signs in the more common respiratory diseases, for those unused to listening to chests. This emphasizes one interesting aspect of the care of the respiratory patient in America in that the respiratory therapists and nurses are expected to record the physical findings 'prior to, during and after therapy' and this would, I think, still be unusual here. Also the statement 'that third party payout may refuse to reimburse the hospital for unmonitored treatments' is somewhat thought-provoking.

The X-ray section is intelligible to the beginner in this study and, for the experienced, gives an organized summary of radiological chest material. There is a résumé of the different radiological techniques and positions possible to use and notes with accompanying X-rays of most of the common lung diseases including iatrogenic ones.

There is a good account of the interaction of aerosols and humidified air with the respiratory tract, with a description of the clearance mechanisms of the lungs including anatomy and physiology of the factors chainging the normal function. There is a chapter giving greater detail of the use of aerosols in respiratory care, the first part emphasizing the physical aspect and the second the clinical, so that there is some duplication between the two chapters.

Infection in Respiratory Therapy is dealt with in detail with some excellent colour plates of various organisms and considerable emphasis on the collection and transport of specimens and evaluating the sputum. There are a few useful pages on the principles of controlling the spread of infection generally and in intensive care units.

The chapter on drugs used in respiratory care deals mainly with their use from the respiratory therapist's point of view but gives a brief résumé of the most commonly used respiratory drugs under, of course, their American names.

The clinical aspect of the book is once again emphasized in Tubes, Techniques and Procedures. A great deal of this is elementary but useful: endotracheal tubes, tracheostomy tubes, chest drains, arterial lines and venous lines are all covered with care and problems discussed.

Intermittent positive-pressure breathing, which covers much of the daily activity of the respiratory therapist, is dealt with in considerable detail. Definition, effects, indications, hazards and contra-indications are covered. The chapter also tries to establish, with only moderate success, some scientific justifications for this procedure which 5–10% of all patients in American hospitals receive!

Mechanical ventilation is dealt with concisely and adequately; a brief history of ventilation, classification of ventilators, indications for, techniques and complications of mechanical ventilation are amongst the topics. There is an excellent performance analysis of a wide range of ventilators with a most useful 'trouble-shooting' paragraph on each one.

The third section of this book deals with respiratory care in specific conditions. It starts with the differential diagnosis of the various obstructive pulmonary diseases, from the nasal passages through chronic bronchitis, asthma, emphysema and bronchiectasis, to small airways disease. In the following chapters, respiratory aspects of myocardial infarction, congestive heart failure, a wide range of neurological and neurosurgical conditions, the adult respiratory distress syndrome and the postoperative or traumatized patients are covered succinctly and practically.

A large part of this section is devoted to specific neonatal and paediatric respiratory problems. In the rest of the book these areas have only been briefly mentioned. Here, however, fetal lung development, functional changes at birth and neonatal resuscitation are given importance and there is an excellent detailed description of intubation of the neonate. The neonatal respiratory distress syndrome is discussed fully, as are a wide range of other disorders producing respiratory problems in the neonate. The paediatric section is mostly given over to a detailed coverage of asthma and cystic fibrosis, including clinical, pathological and physiological aspects and forms of treatment.

The final chapters in this book deal lucidly with cardiopulmonary resuscitation and patient monitoring and give all the basic information necessary to deal with a cardiac arrest and the further monitoring of the patient for even the most inexperienced in this area. There are four appendices giving useful normal values of pulmonary function tests, a suction protocol, a résumé of gas laws and medical abbreviations.

This is a well produced volume and a consistent standard is maintained throughout. The illustrations, tables and photographic plates are good. There are numerous references at the end of each section and some have an additional bibliography.

This book will be of interest to those involved in the clinical practice of respiratory care and will be particularly useful to those teaching basic respiratory care.

E. Cornwell

Clinical Aspects of Respiratory Pharmacology

Clarence A. Guenter, Martin H. Welch and James C. Hogg

Philadelphia: Lippincott (Oxford: Blackwell Scientific). 1978. Pp. viii + 177. Price £7.60

This paperback is a reprint of the first four chapters of *Pulmonary Medicine* first published in 1977. The publishers have re-issued it for medical students, nurses, respiratory therapists, and practising physicians 'in response to requests by many readers'.

The chapters review the effect of different atmospheric compositions and pressures on respiration, the physiology of airflow measurements, the theoretical basis of routine lung function testing and the physiology of respiratory gas exchange. The text is clear and well illustrated, the bibliography is extensive.

There are two problems with this book. First, it has inevitably dated since 1975/6 when most of the chapters seem to have been written It is doubtful if the distinguished authors would repeat some of their conclusions today. Secondly, there are some transatlantic views which do not reflect the mainstream of UK clinical pulmonary physiology, particularly the stress on the value of the maximum voluntary ventilation test as opposed to the peak flow rate or FEV_1.

Parts of this book could be read profitably by medical students or housemen, but they would need guidance on which they should be.

P. H. WRIGHT

Respiratory Therapy Pharmacology

Joseph L. Rau, jun.

Chicago and London: Year Book Medical Publishers. 1978. Pp. xii + 149. Price £9.75

This book is aimed at American nurse/technicians who administer respiratory therapy and is based on a pharmacology course given at the College of Allied Health Sciences at Georgia State University. It gives them 21 pages on the general principles of pharmacology, 30 pages on calculating drug dosages, with examples and exercises, and about 85 pages on the pharmacology of the different categories of 'bronchoactive' drugs used in respiratory diseases, as well as neuromuscular blocking agents and prostaglandins. The book assumes virtually no knowledge of physiology or pharmacology, but includes considerable detail of biochemical mechanisms of action, and gives many references to original papers, some published as recently as 1976. It seems unlikely to appeal to respiratory therapy executives in Britain.

A. HERXHEIMER

Lung Biology in Health and Disease, 7. Lung Water and Solute Exchange

Norman C. Staub

New York: Marcel Dekker. 1978. Pp. xiv + 568. Price SFr 135

This is the seventh in an excellent series of monographs designed to cover the most up-to-date information on specific aspects of lung biology in health and disease. The individual chapters are written by acknowledged experts on specific aspects of lung oedema and the whole integrated into book form by one author.

The first four chapters focus on the functional anatomy of the alveolar capillary tissue. The middle portion describes quantitative aspects of lung oedema with emphasis on mechanisms and theories. The final chapters deal with treatment of pathological states. The combination provides an invaluable collection of scientific information which is not available in such concise form in any other book. Despite multiple authorship the style is clear, the format easy to follow and the references comprehensive. I particularly like the clearly drawn diagrams, excellent photographs and full descriptions of each figure. Inevitably some omissions occur; the possible role of cell injury and intracellular oedema is only mentioned briefly.

Nevertheless this book forms essential reading for all with an interest in lung oedema and should be of value to many in other branches of medicine.

W. A. CROSBIE

Status Asthmaticus

Earle B. Weiss

Baltimore: University Park Press (Lancaster: MTP Press). 1978. Pp. xii + 408. Price £14.95

This publication contains the proceedings of a symposium which was held in Boston in the summer of 1977. In spite of careful editing it suffers from the inevitable overlap, repetition and variety of style which follow when multiple authors submit individual contributions. This matters less if the book is used primarily as a source of reference, although then it becomes disappointing to note that some of the lists of references are neither comprehensive nor up-to-date. A series of additional references grouped according to chapter headings has been incorporated at the end of the book by the editor and this fills some of the gaps.

The chapters are gathered into two main sections, Fundamentals and Pathophysiology preceeding Clinical and Therapeutic Considerations. With a few exceptions, the contributions in the first section are good, the chapter on Physiological Changes in the Acute

Asthmatic Attack by Warren R. Summer warranting particular praise. The section on Clinical and Therapeutic Considerations is more patchy: some of the contributions reflect transatlantic differences in drug availability but others are either disappointingly superficial (e.g. Oxygen and Mechanical Ventilation in Status Asthmaticus) or contain inappropriate detail (e.g. renal failure listed as a common complication of status asthmaticus However, it would be a pity to allow these defects to detract from the value of some of the chapters in this section: the authors dealing with Status Asthmaticus in Childhood, The Role of Antibiotics and Corticosteroid Mechanisms and Therapeutic Schedules all provide an excellent account of their respective topics.

At £14.95 per copy, few clinicians will wish to purchase this book but it warrants a place in chest department libraries, although I fear many copies will remain on the shelves for long periods.

M. Branthwaite

Immunomorphology and Immunopathology of the Lung

Alex Eskenasy

Bucarest: Editura Academiei (Tunbridge Wells: Abacus Press). 1978. pp xiv + 313. Price £18.65

This book was first published in Romania in 1972 and has recently been translated into English.

The treatise summarizes the author's major work on experimental models of lung responses, using classical methods of descriptive morphology. It clearly represents a life's work of detailed thought and study and as the author notes in the preface to the English edition it 'draws attention to the work being carried out in Romania in pulmonary immunopathology'. The approach to the subject, following the teachings of the great continental histopathology morphologists of the 19th century, is very different from that of many parts of the English speaking world and for this reason is worth noticing. It may stimulate new ideas for those studying in great depth certain individual lung cells, especially in animal models, and especially in those who have had a very different type of training in pathology. Otherwise it is not likely that the book will attract a wide readership. The translation has obviously provided problems and it is difficult to sort out theory, philosophy and observation from the rather wordy text.

It has to be recognized and appreciated that this book is intended essentially as a monograph summarizing the author's own observation, together with an additional attempt to draw attention to the studies of others less well known in English-speaking countries; it is important to recognize the value of some of these less familiar studies.

It has, however, a limited broader value, partly because there are so few recent references and partly because it largely ignores many of the outstanding contributions to the understanding of immunology and immunopathology of the lung which have originated from other parts of the world.

In summary it is difficult to find common ground between the contents of this book and modern immunopathological thinking in many other countries, and in this an educational opportunity has been lost.

M. Turner-Warwick

Lung Biology in Health and Disease, 8. Extrapulmonary Manifestations of Respiratory Disease

Eugene Debs Robin

New York: Marcel Dekker. 1978. pp. xviii + 516. Price SFr 134

Volume 8 of this series for the wealthy could be better titled. It in fact contains 13 authoritative reviews of different aspects of body function and how they are affected by the changes associated with lung disease. All the chapters are by groups actively working in the fields they describe. If too many chapters consist of attempts to reconcile conflicting papers which pose more questions than they answer, it is because the fields covered are growing rapidly, making reviews of this type even more helpful.

The book is in three parts. The first deals with abnormalities of P_{O_2}. Chapter 1 reviews the reaction of oxygen and haemoglobin, covering the effects of different haemoglobins and the many other molecules known to affect the oxygenation of the blood. Chapter 2 introduces the problems of analysing biological redox reactions experimentally. Chapter

3 gives a balanced evaluation of the results of attempts to examine intracellular redox reactions. The main problems are, of course, the relationship between these results and processes in intact animals, and that our current methods only measure some of the components of a complex series of reactions with many determining factors. Chapter 4 considers the metabolic changes in ischaemic organs and their potential for adapting to hypoxia and then recovering from it; once again the main problem is to find useful techniques to evaluate this. Chapter 5 reviews the evidence that ambient Po_2 controls the levels of intracellular respiratory enzymes; such an effect could explain the differences between the metabolism of alveolar and systemic macrophages. Chapter 6 discusses disorders associated with mitochondrial dysfunction; the commonest are thyroid disorders though the mechanism is unknown. Chapter 7 tells how oxygen toxicity increases intracellular superoxide and hydroperoxide levels, which in turn selectively damage cellular enzymes. C. J. Lambersten gives a masterly review of oxygen toxicity in Chapter 8, stressing the importance of time and level in predicting adverse effects, and the increased tolerance to hyperoxia with intermittent exposure.

Part 2 deals with carbon dioxide and pH. Chapter 9 discusses CO_2 exchange and buffering. Even here our knowledge is painfully thin; we still do not know why the Enghoff tenet is untrue. Chapter 10 covers the effect of pH changes on metabolic enzymes, and Chapter 11 the effects on individual organs and tissues and their local pH.

Part 3 briefly covers the relationships between pulmonary and systemic immune resposes. Chapter 12 is on the immediate hypersensitivity reactions, and Chapter 13 on immunoglobulin metabolism.

This is a useful book which is well edited and produced. It would be of value to those working in the fields covered and with the necessary basic knowledge of metabolism. Books of this kind inevitably become dated quickly. Departments whose research is not in this area may not find its cost justified.

P. H. Wright

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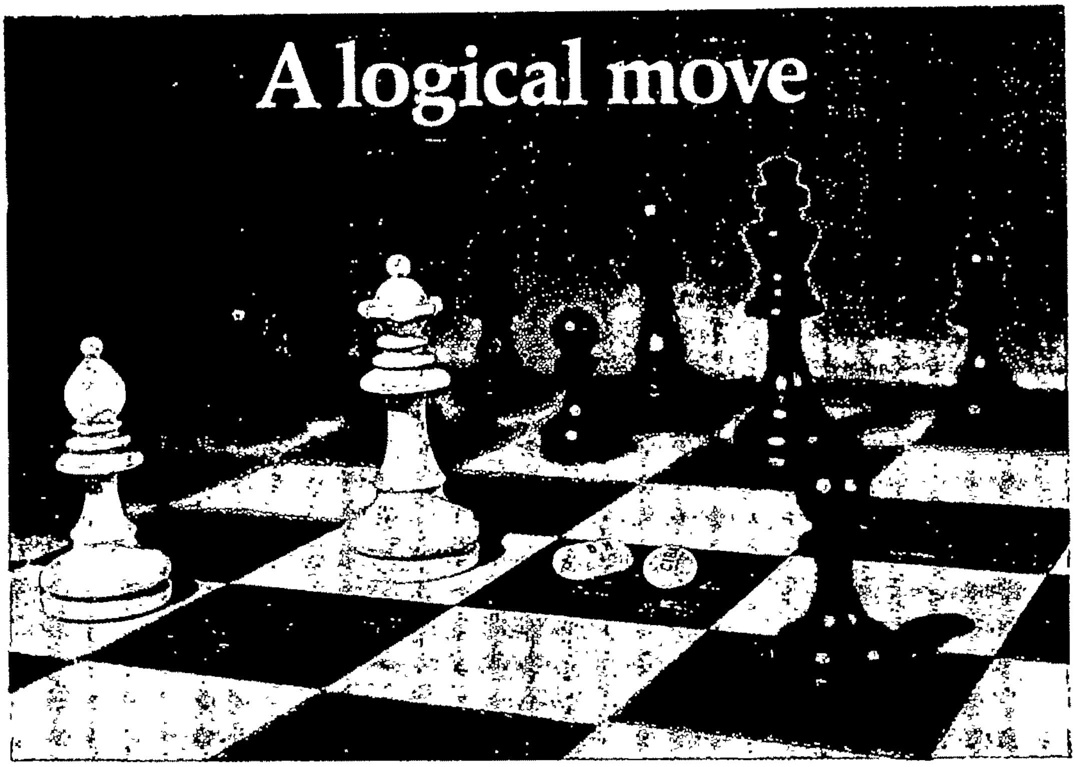

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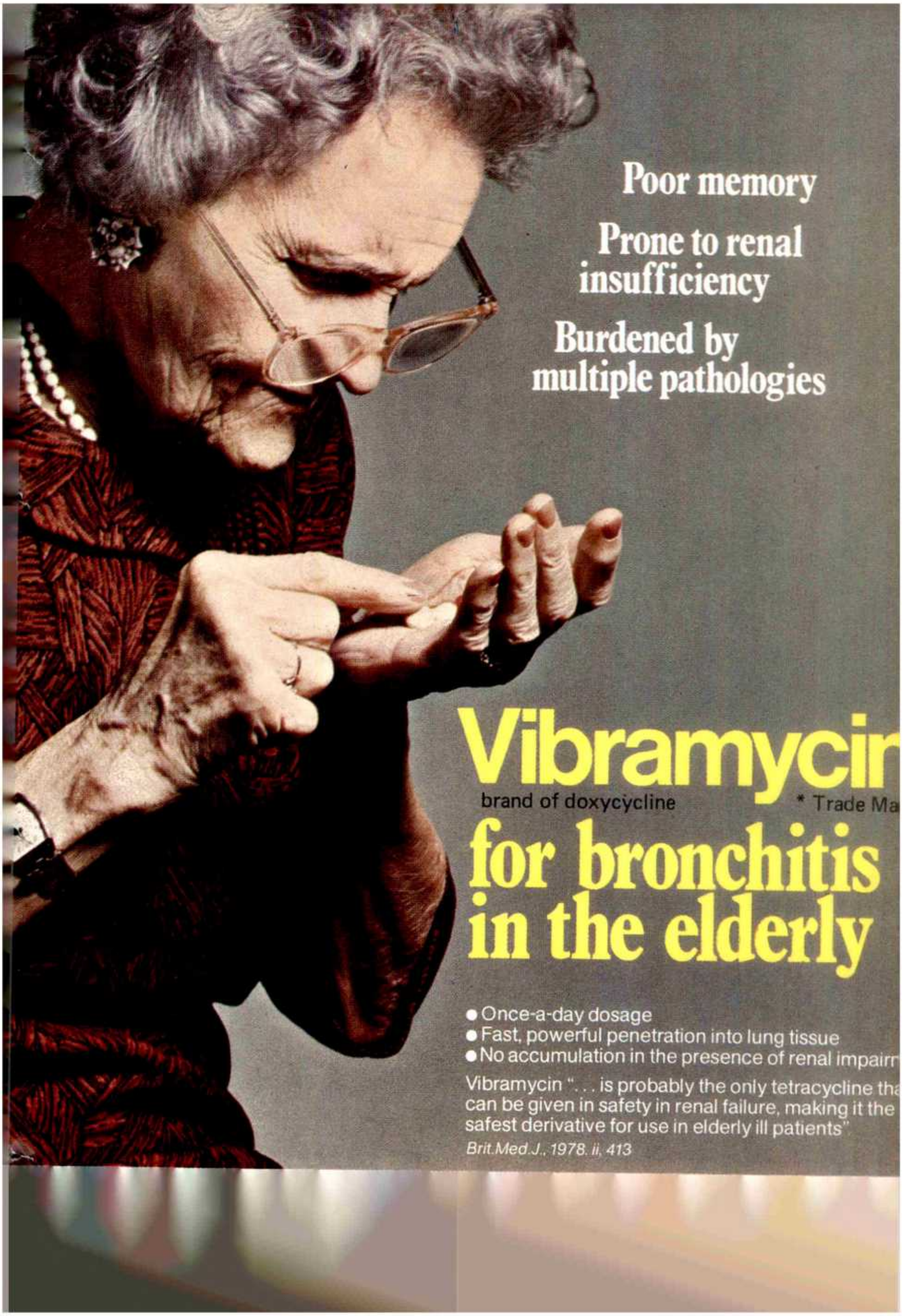

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Review Article

SMALL-CELL LUNG CANCER: A CURABLE DISEASE?

ANDREW M. ARNOLD AND CHRISTOPHER J. WILLIAMS

CRC Medical Oncology Unit, Southampton General Hospital,
Southampton University, England

Barnard (1926) was the first to recognize that the so called 'oat-celled sarcoma of the mediastinum' was in fact a primary malignant tumour of the bronchus. Despite this, it was not until Azzopardi (1959) and Watson and Berg (1962) published reviews of large series that the distinctive clinical presentation, course and response to treatment of small-cell carcinoma of the lung was clearly demarcated from that of other main types of bronchial carcinoma. Even today, despite 20 years of increasing awareness of the disease, some clinicians fail to make a distinction between this and other types of lung cancer.

Over the past few years a vast literature has accumulated on all aspects of the disease and the reader is referred to several recent reviews (Bunn et al. 1977; Greco et al. 1978*a*; Livingston 1978). Because of its comparative sensitivity to modern chemotherapeutic agents it is one of the most challenging tumours for the medical oncologist. Recent publications suggest that prolonged disease-free survival and possibly cure may be achieved in a selected group of patients (Greco et al. 1978*b*) but despite this progress there is still considerable confusion and nihilism concerning the best way to manage patients with the disease. This paper will outline some of the new concepts that have led to an increasing median survival.

PATHOLOGY

In the classification of lung cancers proposed by Kreyberg (1967) for the WHO, small-cell anaplastic bronchial carcinoma is classified into four subtypes (Table 1), oat-cell being one of the subtypes. The Lung Cancer Working Party (Mathews 1973) suggested that the subtyping was an artificial separation as polygonal cells, fusiform cells and other types were sometimes seen in different areas of the same tumour. They therefore suggested a simplified classification (Table I).

Further evidence that the separation of small cell carcinoma of the lung into subtypes is artificial is provided in a study of 53 patients (Mathews et al. 1977) among whom there was no significant difference in the natural history or response to therapy by different subtype. For accuracy the term small-cell carcinoma of the lung should be used in preference to the older historic term oat-cell carcinoma.

The histological classification described above has evolved over many years and it should not be assumed that the histology reported in early studies correlates with the current classification. Using the WHO classification, Yesner et al. (1973) reviewed 449 patho-

Table I. Classification of bronchogenic carcinoma

	WHO		*WPL*
I	Epidermoid (squamous)	10	Epidermoid
II	Small-cell anaplastic 1. Fusiform 2. Polygonal 3. Lymphocyte-like 4. Others	20	Small-cell anaplastic *a.* Lymphocyte-like (oat cell) *b.* Intermediate cell (fusiform polygonal cell and others).
III	Adenocarcinoma	30	Adenocarcinoma
IV	Large-cell carcinoma	40	Large-cell carcinoma

logical specimens and found 98 small-cell carcinomas of which only 30 had been diagnosed previously.

CELL OF ORIGIN

Both small-cell carcinoma and bronchial carcinoid are thought to arise from neoplastic transformation of the Kulchitsky or K cell which lies deep in the bronchial mucosa (Bensch et al. 1965; Pearse 1969; Smith 1975). The most characteristic feature of the K cell, demonstrated by electron microscopy, is the presence of neurosecretory granules—the storage sites of small polypeptide hormones and other active amines. Their function in the lung is unknown, but there is speculation that they may be concerned with the vasoconstrictor response to hypoxaemia (Hernandez-Vasquez et al. 1977). They can be demonstrated by special histochemical techniques and occur in greatest number in fetal and newborn lungs (Hage 1972; Tateishi 1973). Carcinoids may be mistaken for small-cell carcinoma, particularly when diagnosis is made from inadequate biopsy specimens (Bensch et al. 1968; Smith 1975). Despite a common origin, the two tumours are probably epidemiologically unrelated (Godwin & Brown 1977), small cell carcinomas of the lung being related to cigarette smoking (although occasionally it occurs in non-smokers), carcinoid often occurring in young non-smokers (Tischler 1978).

The K cell is probably a member of the APUD (amine precursor uptake and decarboxylation) series of cells (Pearse 1968) and small-cell carcinoma is therefore considered to be an apudoma. If the APUD cell concept is correct, small-cell carcinoma of the lung is embryologically related to other tumours, e.g. medullary carcinoma of the thyroid and phaeochromocytoma, which arise from cells having their origin in the neural crest (Weichert 1969). Although these tumours arise in widely differing areas of the body they have remarkably similar ultrastructural and histochemical characteristics (Pearse 1969) and are also commonly associated with the production of ectopic hormones.

In patients with small-cell carcinoma of the lung the incidence of ectopic hormone syndromes varies greatly and depends on the criteria used for diagnosis and the degree of suspicion of the individual clinician. The diagnosis may be made on clinical, biochemical and histological grounds. Kato et al. (1969) used clinical criteria alone to diagnose ectopic ACTH syndromes in 2.8% of patients with small-cell carcinoma of the lung. Gilby et al. (1975), using biochemical criteria, demonstrated that dexamethasone was unable to suppress raised midnight plasma cortisol levels in 51% of the patients with small-cell carcinoma of the lung. Bloomfield et al. (1977), using radio-immunoassay and histochemical techniques, found biologically and immunologically active ACTH in all lung cancer tissue with carcinoid or oat-cell features and a striking relationship between the presence of secreting granules and plasma ACTH levels. The clinical relevance of the diagnosis when made by such special investigations is, however, not known.

Nearly 20 different tumour products are now known to be associated with small-cell carcinoma of the lung (Table II) but none have emerged as useful markers for this disease. The subject has been extensively covered in two recent reviews (Coombes et al. 1978; Richardson et al. 1978).

Table II. Tumour products associated with small-cell carcinoma of the lung

ACTH	Histaminase
ADH	5-HT
GH	Renin
Calcitonin	Serotonin
FSH	Erythropoiesis supressor
LH	Neurophysins
HPL	Vasoctive intestinal polypeptide
MSH	

DIAGNOSIS

With the advent of effective non-surgical treatment for small-cell carcinoma of the lung the importance of obtaining a histological diagnosis in all types of lung cancer cannot be over-stressed. Certain clinical features should alert the physician that a patient may have small-cell carcinoma rather than other cell types (Fig. 1). Some 80% of patients have symptoms for less than three months (Kato et al. 1969) and superior vena caval obstruction is more than twice as common in small-cell carcinoma as in any other type (Polackwich & Straus 1977). Similarly the patient presenting with bulky cervical or supraclavicular lymphadenopathy is more likely to have small-cell carcinoma of the lung. Radiological features suggestive of small-cell carcinoma of the lung are a central tumour mass associated with hilar nodes and mediastinal widening, which occurred together in 64% of patients in one study (Cohen & Mathews 1978). Squamous-cell carcinoma also is associated with a central mass in the majority of cases, but mediastinal extension is less common and symptoms often are present for much longer, averaging eight months in one large series (Carlisle et al. 1951).

The fibreoptic bronchoscope has led to an increased yield of positive endoscopies and its role has been adequately discussed (Struve-Christensen et al. 1974; Sackner 1975; Zavala 1975). Because of the central location of the majority of tumours a positive biopsy should be obtained in most patients. One recognized disadvantage of the

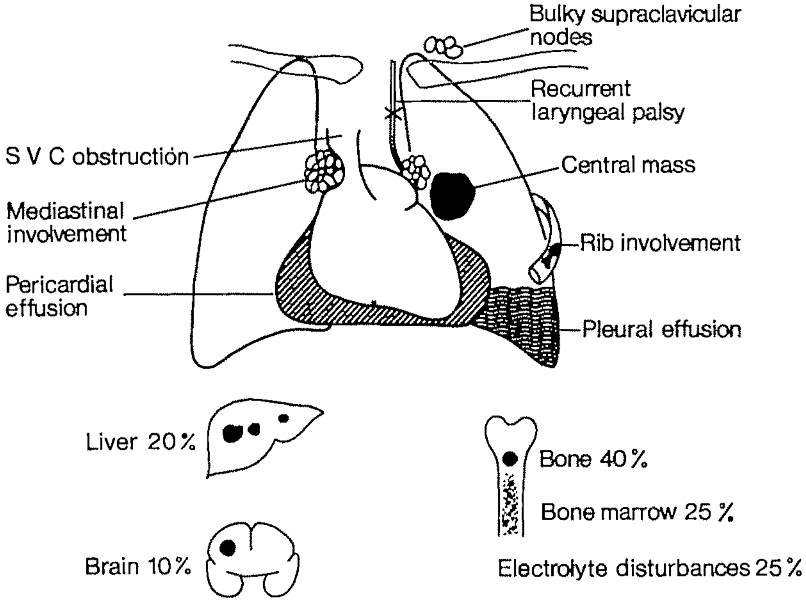

Fig. 1. Local and metastatic manifestations of small-cell carcinoma of the lung at the time of presentation

fibreoptic bronchoscope is the small size of the biopsy and the considerable crush artefact that can occur. Brush or sponge biopsy is useful, but it must be remembered that small-cell carcinoma usually arises deep in the mucosal layer and may be entirely covered by normal epithelial cells and thus missed if this technique is used alone.

Some 20% of patients with small-cell carcinoma of the lung have only a peripheral mass with or without hilar and mediastinal widening and in this small group of patients transbronchial biopsy via the fibreoptic bronchoscope or transthoracic needle biopsy under radioscopic control will usually provide the diagnosis.

Although an 'invasive' procedure, cervical, supraclavicular or mediastinal lymph node biopsy may often be the quickest way to obtain an answer and can usually be performed under local anaesthetic. Where the diagnostic and clinical expertise is available percutaneous needle biopsy of a superficial node can be almost as accurate as an open biopsy. Lymph node biopsy should be considered whenever other techniques have given an equivocal diagnosis.

Once pathological material has been obtained the cytological and histological interpretation may still pose a problem. Although Lukeman (1973) found that there are very few false positives and false negatives when a definite cytological diagnosis of lung cancer has been made, he found that the specificity of cell type correlated far less well. Fortunately, in small-cell carcinoma of the lung the diagnostic accuracy of specific cell type (86%) by cytology was greater than for most other subtypes of cancer. The overall accuracy of histological and cytological methods of diagnosis was 85% in a series comparing autopsy findings with the initial diagnosis (Yesner 1973).

Where the histological diagnosis is still in doubt after using light microscopy and conventional histochemical techniques, the electron microscope may be of value by demonstrating the presence of neurosecretory granules. In the future newer techniques such as immunoperoxidase staining may identify certain specific intracellular substances, e.g. precursor amines.

STAGING

The main benefit of staging is seen when it can be shown that choice of treatment according to stage improves survival; Hodgkin's disease provides a good example of this (Kaplan 1976). Staging also gives a more complete knowledge of the sites of disease and if investigations originally positive are repeated and found to be negative then a decision to stop therapy may be made with greater confidence. This approach has been used to advantage for the management of diffuse histiocytic lymphoma and more recently for ovarian carcinoma (DeVita et al. 1975; Young et al. 1978).

The most commonly used system for staging patients with small-cell carcinoma of the lung is the limited/extensive system (Table III). More complex systems such as the TNM systems have been assessed, but have been found to be of little value (Mountain et al. 1974).

Table III. Limited/extensive staging

Limited disease	Disease confined to one hemithorax but including ipsilateral mediastinal, scalene and lower cervical nodes*
Extensive disease	All disease not defined above

* Some workers now put patients with cytology-positive pleural effusions into the extensive disease group.

In small-cell carcinoma of the lung much information has been gathered on the natural history of the disease and only a few clinicians would still accept that it should be managed by local treatment alone. Most of the credit for our knowledge of metastatic sites must go to the meticulous studies of such workers as Hansen in Denmark and Mathews in the USA who have summarized their work in two reviews (Cohen & Mathews 1978; Hansen et al. 1978).

The value of such extensive staging techniques as bone marrow biopsy and liver biopsy via the peritoneoscope is questioned by many who argue that, as the disease is nearly always disseminated, they are unnecessarily invasive and wasteful of resources.

However, numerous trials have shown that patients with limited disease survive longer than those with extensive disease whatever therapy is given (Roswit et al. 1968; Green et al. 1969; Holoye et al. 1977; Livingston et al. 1978). As will be discussed in a later section, it is among the patients with limited disease that nearly all the long-term survivors are found and it is with this minority group that current hopes of curative therapy lie. The therapies advocated with curative intent are intense, toxic and usually multimodal. Staging may thus be important to exclude the majority of patients from this aggressive type of therapy.

While not necessarily advocating the routine use of all the techniques outlined below, we now describe the commonest sites involved and the methods of staging.

Bone marrow

The incidence of bone marrow involvement varies, but the overall incidence from 10 series was 143/617 (23%) (Hansen et al. 1978). Hirsch et al. (1977) postulate that the gradual reduction in the incidence of bone marrow involvement in recent series is a reflection of earlier referral of patients. Reliance on haematological abnormalities is a poor indication of bone marrow involvement; however, where a leucoerythroblastic change was present, eight of nine patients from a series of 203 (Hirsch et al. 1977) had bone marrow involvement. A further 25 patients in the series had a near normal blood examination in the presence of marrow infiltration.

Bone marrow aspiration would appear to be superior to trephine biopsy, but the investigations are complementary. The value of bone marrow examination must be viewed with the knowledge that 75% of patients with bone marrow secondaries found on aspiration have no other evidence of distant metastases if the procedure of liver biopsy via a peritoneoscope is excluded from the diagnostic workup (see below). Furthermore, knowledge of the state of the bone marrow aids the clinician in deciding if unexpected pancytopenia is due to chemotherapy or replacement by tumour.

Intra-abdominal extension

Simple liver function tests may be misleading because of an increased incidence of cirrhosis and other chronic liver diseases in patients with small-cell carcinoma of the lung (Margolis et al. 1974). However, in one autopsy series where all three liver function tests were abnormal (alkaline phosphatase, SGOT and LDH) 86% of patients had liver metastases (Gutierrez et al. 1975). Newer techniques such as grey-scale ultrasonography and computerized tomography are likely to replace radio-isotope scanning in the future. Numerous false positives occur with radio-isotope scanning and the liver scan is unlikely to detect small metastatic deposits.

Dombernowsky et al. (1978) advocated the procedure of peritoneoscopy with liver biopsy under direct vision. In a series of 190 untreated patients, metastatic hepatic disease was detected in 21% with this technique; 41% of the total had no other evidence of extrapulmonary spread, 35% also had bone marrow involvement and 24% had other signs of extensive disease. Although a highly valuable research tool, this procedure does not help in the management of most patients.

In addition to liver metastases, autopsy studies show extension to the kidneys (22%), adrenals (39%), pancreas (31%) and abdominal lymph nodes (57%) (Hansen 1974).

Extent of thoracic disease

If surgery is to be contemplated the surgeon must go to lengths to exclude inoperability. New data accumulating from the use of computerized tomography of the chest have shown that virtually all patients who might otherwise appear to have operable disease have widespread intrathoracic disease. Unnecessary thoractomy could be avoided if this technique was more readily available.

CNS disease

Collected studies show that 17 of 171 patients with small-cell carcinoma of the lung had brain involvement at the time of diagnosis (Eagan et al. 1974; Newman & Hansen

1974; Abeloff et al. 1976; Einhorn et al. 1976). It has been estimated that 25% of patients with small-cell carcinoma of the lung develop clinical evidence of brain extension during the course of their disease (Eagan et al. 1974; Holoye & Samuels 1975; Einhorn et al. 1976; Bunn et al. 1978) and post-mortem studies have shown that 40% of patients have evidence of brain extension (Halpert et al. 1960; Fine & Deely 1971; Auerbach et al. 1975; Mathews 1976; Bunn et al. 1978).

The isotope brain scan has been the standard but rather insensitive investigation used to detect brain metastases. Where clinical signs are absent it is positive in only about 4% of patients (Bunn et al. 1978). However, if there are symptoms it is positive in 95% of patients. Computerized axial tomography has an almost 100% accuracy. The role of the CT scan in detecting subclinical disease has yet to be assessed.

Recently, as median survival has improved and cranial metastases appear to be reduced or delayed by prophylactic cranial irradiation (see below), spinal and leptomeningeal metastases have emerged as a not insignificant site of relapse. Small-cell carcinoma of the lung accounts for more than half the cases of carcinomatous leptomeningitis due to lung cancer (Olsen et al. 1974) and the incidence in one autopsy study was 28% (Nugent et al. 1978).

PROGNOSTIC FACTORS

When planning or interpreting the results of clinical trials careful attention must be paid to the distribution between treatment groups of the important prognostic factors. Acknowledge of these factors is also important when trying to choose the best treatment for an individual patient.

Extent of disease

The extent of disease is probably the most important factor in determining both response to therapy and survival (Table IV). Though more complex staging systems are

Table IV. Complete response and disease extent

Reference	*Stage*	*No.*	*Complete response* (%)	*Median survival* (months)
Livingston et al. (1978)	Limited	108	41	12
	Extensive	250	14	7
Johnson et al. (1978)	Limited	35	75	18+
	Extensive	36	40	10
Einhorn et al. (1978)	Limited	19	89	20
	Extensive	39	22	9
Greco et al. (1978*b*)	Limited	16	94	14+
	Extensive	20	15	11
Greco et al. (1978*a*)	Limited	32	96	16+
Cohen et al. (1978)	Limited	19	74	16+
	Extensive	42	42	10

available, most trials reported have used the simpler limited/extensive disease system discussed previously. All trials reported to date have shown that those patients treated for limited disease are more likely to respond to therapy (approximately 60% *vs.* 30%) and to survive longer (median survival 1–1½ years *vs.* nine months) when compared with patients treated for extensive disease.

General health

Karnofsky et al. (1948) was the first to point out the prognostic importance of general health at presentation, which is particularly evident in lung cancer, and several assessment scales are currently in use. Karnofsky's scale is shown in Table V. All the major series reported have shown markedly higher response rates and longer survival in ambulatory patients when compared with non-ambulatory patients, regardless of the stage at presentation. Many studies, quite rightly, exclude patients with poor performance status but this must be taken into account when interpreting results.

Table V. Karnofsky scale for performance status

Able to carry on normal activity; no special care is needed	10.	Normal, no complaints, no evidence of disease
	9.	Able to carry on normal activity, minor signs or symptoms of disease
	8.	Normal activity with effort, some signs or symptoms of disease
Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed	7.	Cares for self, unable to carry on normal activity, or do active work
	6.	Requires occasional assistance, but is able to care for most of his needs
	5.	Requires considerable assistance and frequent medical care
Unable to care for self, requires equivalent of institutional or hospital care; disease may be progressing rapidly	4.	Disabled, requires special care and assistance
	3.	Severely disabled, hospitalization is indicated, although death not imminent
	2.	Very sick, hospitalization necessary, active supportive treatment necessary
	1.	Moribund, fatal processes progressing rapidly
	0.	Dead

Sex

In one cooperative study (Edmonson et al. 1976) women survived significantly longer than men, though this has not been shown in other studies.

Although performance status and disease extent are currently the only major factors influencing response to treatment, the effect of disease in various metastatic sites should be carefully studied. Metastases to the skin, lymph nodes and bone marrow appear to respond better than those to liver and bone.

SURGERY

Large surgical series (Mountain 1974; Selawry & Hansen 1974), including that of the Medical Research Council of Great Britain (Fox & Scadding 1973), have reported five-year survivals of less than 1% for patients undergoing potentially curative resection. It has therefore been stated that excisional surgery has no part to play in the management of this tumour. Other studies have reported five-year survivals of up to 10% and have advocated surgery (Lennox et al. 1968; Compobasso et al. 1974).

Many of these series were undertaken at a time when a widely accepted histological classification of lung cancer was not available, so that the diagnosis of small-cell carcinoma of the lung may not have been uniform. In addition, some of these studies are retrospective and many inadequately staged by modern criteria.

The VA-Armed Forces' Cooperative Study of surgical resection (Higgins et al. 1975) for symptom-free patients with peripheral small-cell carcinoma of the lung reported a five-year survival of 36%, suggesting that the failure of surgery is an outcome of our inability to detect the extent of the disease at the time of surgery.

If there is a role for surgery in small-cell carcinoma of the lung it can only be in those patients shown to have localized disease by present staging techniques and found to be resectable by current criteria after mediastinoscopy. Even in these cases, surgery should probably be considered only in combination with chemotherapy. Such patients will be uncommon; more than 70% of patients staged have extensive disease and of those considered for surgery Sarin and Nohl-Oser (1969) found mediastinal involvement in 75% of patients with small-cell carcinoma of the lung compared with 35% in patients with squamous-cell tumours. Goldberg et al. (1970) found evidence of contralateral spread by mediastinoscopy in 6% of patients with squamous-cell carcinoma, but in 50% of those with small-cell carcinoma of the lung.

In patients undergoing surgery the postoperative mortality rate for patients with small-cell carcinoma of the lung is about 10% (Lennox et al. 1968; Fox & Scadding 1973; Campobasso et al. 1974; Selawry & Hansen 1974). If surgical resection is limited to those patients who have proved localized disease and better health grading the postoperative mortality rate may be lower.

Future trials may explore the role of surgery with chemotherapy in patients with minimal localized disease. The use of surgery alone for patients who are symptom-free with peripheral lesions still results in a 64% five-year mortality (Higgins et al. 1975), suggesting the importance of systemic therapy in addition to resection. Such studies would require a multi-centre trial to ensure sufficient numbers of patients and careful stratification for all known prognostic factors would be necessary.

RADIOTHERAPY

Radiotherapy, like surgery, can be expected to effect a cure only in patients with strictly local disease, although good palliation can often be achieved if metastatic sites are accurately localized. Analysis of radiotherapy trials should include details of total dose, dose fractionation, fields irradiated and type of equipment used. Extent of disease, staging methods employed and health grading should also be reported.

After irradiation, autopsy studies or examination of specimens removed at surgery can be used to estimate effectiveness of the total dose. If sterilization of the tumour is the criterion of response, then it has been estimated that the optimal dose levels for patients with varieties of lung cancer other than the small-cell would be above 6000 rads for a 95% sterilization rate. Salazar et al. (1976) state that small-cell carcinoma of the lung is exquisitely sensitive to radiation therapy, but that radiocurability of lung tumours is inversely proportional to their radiosensitivity and decreases with faster rates of growth (decreasing doubling time) (Table VI). However, many irradiated patients will die of disease elsewhere without relapse in irradiated sites.

Table VI. Tumour growth, response to therapy and survival by cell type

Cell type	*Doubling time* (days)	*Objective remission* (%)	*Survival at one year* (%)
Small-cell	30	90	19
Large-cell	86	55	23
Epidermoid	98	41	30
Adenocarcinoma	187	35	32

From Salazar et al. (1976).

Salazar et al. (1976) reported median survival of 5.1 months for patients with small-cell carcinoma of the lung treated by radiation and Roswit et al. (1968) had a 3.3 month survival for such patients. Local relapse is unlikely to be evident if survival is so short.

Williams et al. (1977) reported the effect of sandwich radiotherapy (3000 rads) and chemotherapy in patients with extensive small-cell carcinoma of the lung. Not only was radiotherapy unable to improve survival, it also failed to prevent relapse at irradiated sites. The improved median survival of 10 months in this study may have unmasked the high incidence of local failure after radiotherapy which was not evident in patients surviving shorter periods. They also reported recurrence within the irradiated field in patients with localized disease receiving 4000–5000 rads in a preceding study. Wittes et al. (1977), in a non-randomized study, used a similar radiation schedule (3000 rads) and also reported local relapse at irradiated sites. Though small-cell carcinoma of the lung has been previously regarded as a particularly radiosensitive tumour and 3000 rads in 10 fractions over 14 days has been a common dose schedule, there is little evidence that such radiotherapy is capable of sterilization of tumour and its long-term control.

All patients in the MRC trial (Fox & Scadding 1973) which examined the role of radiotherapy and surgery in small-cell carcinoma of the lung had limited disease using the clinical criteria acceptable at the time. Only three of 73 allocated to a policy of radiotherapy survived five years, with a mean survival of 293 days for the total. Many of these patients would have had metastatic disease by modern staging techniques. As there was no specified treatment plan, the course of radiotherapy differed amongst patients and the interpretation of 'radical radiotherapy' was left to individual radiotherapists. Most patients received a total dose of 3000 rads or more, although it was not possible to know how many patients received a dose (5000 rads) likely to be 'curative' in a majority of patients.

The major problem to be resolved by future randomized trials is how to use radiotherapy to achieve the maximal therapeutic response without compromising the ability to give chemotherapy afterwards. Only when optimal scheduling is established can a proper assessment of a combined approach be made.

CNS irradiation

There is accumulating evidence (Table VII) to suggest that CNS irradiation may prevent or delay CNS metastases. There have now been three randomized studies comprising a total of 230 patients (Jackson et al. 1977; Tulloh et al. 1977; Mathews 1978); 35 of 127 (28%) in the untreated groups developed metastases while only six of 103 (6%) in the treated group developed metastases.

Table VII. Prophylactic cranial irradiation in small-cell carcinoma of the lung

Reference	*Prophylactic cranial irradiation*			*No prophylactic cranial irradiation*		
	No.	CNS relapses	Median survival	No.	CNS relapses	Median survival
Randomized						
Jackson et al. (1977)	14	0	9.8	15	4	7.2
Tulloh et al. (1977)	69	2	8.7	82	15	8.5
Mathews (1978)	20	4	—	30	16	—
Non-randomized (25 studies)						
Bunn et al. (1978)	355	29	—	583	129	—
Total	458	35 (8%)		710	164 (23%)	

No improvement in median survival resulted from prophylactic cranial irradiation in these studies. The use of a median survival is, however, too crude a measurement to identify any gain, as less than 50% of patients are at risk of developing brain extension. Improvement in survival related to cranial irradiation will become evident only if large numbers of patients are 'cured' by systemic therapy (Williams 1978).

Cranial irradiation of up to 3000 rads may be given without significant toxicity. Johnson et al. (1978) reported a reversible neurological syndrome in patients receiving concomitant radiotherapy and chemotherapy. Other studies employing cranial irradiation in small-cell carcinoma of the lung have not recognized a similar syndrome.

CHEMOTHERAPY

Small-cell carcinoma of the lung is usually a disseminated disease at the time of diagnosis and any real hope of progress lies with systemic therapy. Of the four main types of lung cancer it is the most responsive to chemotherapy, although most responses are short-lived.

The aim of chemotherapy, perhaps a truism, is to attain a complete response. Relapses amongst patients thought to attain such a response probably reflect the lack of sensitivity of the methods we use to re-stage patients. Nevertheless, in many diseases, e.g. diffuse histiocytic lymphoma, testicular teratoma, Burkitt's lymphoma or ovarian carcinoma, the attainment of a complete response has been synonomous with prolonged disease-free survival and possibly cure for some patients. Patients who do not respond or who have a partial response usually show little survival benefit.

In the management of small-cell carcinoma of the lung we are currently entering an era where a complete response is achieved in the majority of patients with limited disease. About 25% of patients with extensive disease also obtain a complete response though many of these patients relapse within the first year. The majority of patients with limited disease relapse by the second year. However, Greco et al. (1978*a*) reviewed ten recently published series which utilized current intensive regimens and found 42 of 255 (17%) patients with limited disease to be relapse-free two years after achieving complete remission. Longer survival, although still rare, is being reported with increasing frequency and has led to the belief that some of these patients may be cured. Further follow-up will be necessary before this can be ascertained with certainty. However, these survivors represent a highly selected group of patients and these figures do not yet compare favourably with the results obtained by surgery alone in other types of lung cancer.

Single agent therapy

Small-cell carcinoma is a highly responsive tumour and many drugs when used alone can produce objective tumour regression. The most active drugs are listed in Table VIII. Despite objections to amassing data in such a manner, these tables remain a useful means of assessing the relative merits of single agents. It is likely that other agents may also be active but they have not been systematically tested and the data are therefore not available.

Table VIII. Drug activity in small-cell carcinoma of the lung

Drug	*No. responses/ No. evaluable*	*Response rate* (%)	*Complete response* (%)
VP 16–213	85/197	43	7
Vincristine	18/43	42	7
Nitrogen mustard	31/80	39	—
Methotrexate	31/79	39	—
Hexamethylmelamine	24/67	36	7
Cyclophosphamide	52/189	28	4
Adriamycin	12/48	25	4
Procarbazine	11/44	25	—
CCNU	11/76	14	4

In the only randomized study of a single agent versus a placebo (Green et al. 1969) in patients with small-cell carcinoma of the lung, those receiving cyclophosphamide had a significantly prolonged median survival (4.0 months *vs.* 1.2 months). Single agent therapy, with very few exceptions, can not produce a complete response and, as in other tumours, combination chemotherapy is used. Before discussing aspects of combination therapy several newer drugs will be briefly reviewed as they will be increasingly used in the future.

VP 16–213. VP 16–213 is a semisynthetic derivative of podophyllotoxin, a natural product from the root of the May Apple tree. Its mode of action is unknown but it is known to inhibit nucleoside transport and induce single-stranded breaks in DNA. Data is accumulating to show that it is the most active agent yet used in the management of small-cell carcinoma of the lung with a single agent response of 43% (Arnold 1979). Several complete responses have been obtained using this agent alone (Tucker et al. 1978). It is relatively non-toxic, has no cumulative effects and has the advantage of oral as well as intravenous administration. It is thus a strong candidate for inclusion in combination with other drugs.

Hexamethylmelamine. There has been renewed interest in this drug, although it was almost rejected as an anti-tumour agent owing to its low activity in animal models. Recent clinical studies have shown activity in lung cancer with a 36% response rate in small-cell carcinoma of the lung. The drug is given orally usually over a period of about two weeks. Gastrointestinal side-effects are considerable and often dose-limiting.

Methotrexate with folinic acid rescue. This drug has a single-agent response rate of 39% when used in conventional doses. Interest has recently centred around a possible increase in the therapeutic index when given in high dosage followed by 'rescue' with folinic acid (Bleyer 1977). The response rate to this mode of therapy has not been reported for small-cell carcinoma of the lung and no randomized trials have compared high-dose methotrexate and folinic acid rescue with conventional low-dose administration. Methotrexate with folinic acid rescue is potentially attractive as, when administered carefully, bone marrow depression does not occur.

Adriamycin. The drug has now been available for about 10 years but has only recently been incorporated in combination schedules for small-cell carcinoma of the lung. A major problem encountered with this drug is the enhancement of radiation toxicity when they are given concurrently (Johnson et al. 1976).

Combination chemotherapy

Despite the lack of controlled trials, the improvement in response rates and survival achieved with combination chemotherapy over single-agent therapy has led to its acceptance as standard treatment. The mean complete response rate for single-agent therapy is 2.6% (Broder et al. 1977) whilst in 1977 the mean complete response rate for patients treated with combination therapy without radiotherapy was 22%. With the addition of radiotherapy the complete response rate rises to 31% (Greco et al. 1978*a*).

Though the side-effects of combination chemotherapy may be considerable such toxicity is probably acceptable when it is remembered that the postoperative mortality is about 10% and that virtually all patients die rapidly without chemotherapy. Patients achieving a complete response have definite prolongation of survival and erradicaton of disease may be achieved in a few cases. Objective responses, if they are going to occur, will be seen by the eighth week (usually two to three cycles) and patients responding poorly to chemotherapy can be withdrawn at an early stage. Unless a patient has a very poor health grading it is nearly always worth giving a trial of chemotherapy.

No one combination has emerged as being superior and there is a lack of randomized controlled trials: some recent combinations are summarized in Table IX.

One reason for the recent improvement in response rates may be the intensification of the early induction period. This may be achieved in several ways.

Table IX. Recent results of combination chemotherapy of small-cell carcinoma of the lung

Reference	*Drugs*	*No.*	*Responses* (%)	*Complete response* (%)	*Limited disease* (%)	*Median survival* (months)	
						Limited	Extensive
Cohen et al. (1977*b*)	Cyclophosphamide Methotrexate CCNU	23	96	30	17	10.5	
Einhorn et al. (1978)	Cyclophosphamide Adriamycin Vincristine CCNU Methotrexate with radiotherapy	58	89	41	33	19	9
Greco et al. (1978*a*)	Cyclophosphamide Adriamycin Vincristine with radiotherapy	36	—	72	44	14	11
Johnson et al. (1978)	Cyclophosphamide Adriamycin Vincristine with radiotherapy	71	69	58	51	18+	10
Livingston et al. (1978)	Cyclophosphamide Adriamycin Vincristine Methotrexate with radiotherapy	358	—	22	30	12	7

Increasing the number of drugs administered. It has been estimated that the optimum number of drugs for use in combination chemotherapy of small-cell carcinoma of the bronchus is three or four (Bunn et al. 1977). Large numbers of drugs become less manageable, especially in unskilled hands. Most combinations in use today are arrived at empirically. In the future we may test in man optimal combinations and schedules derived from trial in animals.

Increasing the dose of drugs administered. Cohen et al. (1977*b*) in a study at the National Cancer Institute demonstrated that by increasing the dose of a three drug combination of cyclophosphamide, methotrexate and CCNU, the complete response rate rose from 0% to 30% and median survival increased from five months to 10.5 months. For those patients achieving a complete response the median survival was 20+ months.

Decreasing the interval between drug administration. One approach is to repeat the chemotherapy immediately the blood count returns to normal, rather than waiting for the conventional three weeks. Another way may be to administer non-myelotoxic drugs during the period of marrow depression. Vincristine and methotrexate with folinic acid rescue are suitable drugs for this approach.

The use of alternating non-cross-resistant regimens may also increase the response rate. Cohen et al. (1978) administered cyclophosphamide, methotrexate and CCNU over five weeks and then two cycles of vincristine, adriamycin and procarbazine. After the first three-drug combination the complete response rate for limited disease was 42% and 24% for those with extensive disease. At 12 weeks it was 74% and 40% respectively. The addition of a third regimen did not increase the response rate further. This study was uncontrolled so it is not possible to determine the response rate which may have been achieved had either regimen alone been continued for 12 weeks.

Combined chemotherapy with radiotherapy

Limited disease. Though many trials for the management of limited small-cell carcinoma of the lung include combinations of radiotherapy and chemotherapy, there are few randomized studies examining the role of such treatment.

The randomized trials that are available have tested the use of chemotherapy in addition to radiotherapy. An initial study suggested that the addition of cyclophosphamide to radiotherapy was superior to radiotherapy alone. This finding is supported by a preliminary report of the MRC comparing radiotherapy alone with radiotherapy and combination chemotherapy (Blehan 1977). Unfortunately, staging in this MRC study was clinical and it is highly likely that more patients would have been regarded as having extensive disease had more aggressive staging been performed. If a substantial number of patients with extensive disease were included in this trial of patients with 'limited' disease, it is hardly surprising that the addition of systemic treatment to local therapy was beneficial.

In trials of chemotherapy alone, response rates and durations of survival are comparable to or better than those achieved with either radiotherapy or surgery alone. Whether there is a role for radiotherapy or surgery in limited small-cell carcinoma of the lung should now be tested by new studies.

If radiotherapy is used in the combined modality treatment of localized disease, attempts at sterilizing the tumour must be made. Many trials use radiotherapy in doses which are clearly inadequate in the majority of patients. New approaches to radiotherapy planning and drug scheduling will be required to achieve this goal without unacceptable toxicity.

Johnson et al. (1978), reporting on the use of concomitant radiotherapy (variable doses) and chemotherapy (cyclophosphamide, vincristine and adriamycin), had a 75% complete remission rate for patients with limited disease. After the intensive induction phase, which lasted approximately four months, patients received no further therapy and to date only half have relapsed.

Unfortunately although this was the first study to report such high response rates the toxic complications suffered by many patients would be unacceptable to most clinicians. Seventeen of 71 patients died during treatment (some without evidence of disease at autopsy), there were many episodes of septicaemia and most patients required blood and platelet transfusions. Radiation oesophagitis was a major problem, occurring in all patients. It was severe in some patients, requiring nasogastric or parenteral feeding, and resulted in oesophageal stricture in three.

The radiotherapy dose fractionation used in this study varied markedly between patients and the influence of differences in fractionation has not been reported to date. Adriamycin is a powerful radiosensitizer and its use with radiotherapy possibly explains the high incidence of local toxicity and the high complete remission rate in this study.

More recently Greco et al. (1978*b*) used the same combination of drugs at reduced doses together with concomitant radiotherapy. They obtained almost comparable results with much less toxicity. Undoubtedly one of the major challenges in the near future is how best to combine radiotherapy and chemotherapy. The experience of Johnson et al. (1978) suggests that adriamycin should be avoided. There is good evidence that some drugs, e.g. vincristine, may be given safely at the same time as local radiotherapy.

Extensive disease. Chemotherapy is now accepted as the standard mode of therapy in patients with extensive small-cell carcinoma of the lung. There are few trials testing the role of radiotherapy in addition to chemotherapy in extensive disease.

Williams et al. (1977) found that involved field radiotherapy (3000 rads) to sites of initial disease, after two courses of combination chemotherapy, did not improve the median survival of patients or prevent relapse at these sites. The inclusion of radiotherapy after two cycles of chemotherapy resulted in an excessive delay in starting the third cycle of chemotherapy in this study. Future studies will need to explore the consequences of higher doses of radiotherapy and different ways of combining the two treatments before the use of radiotherapy with chemotherapy can be fully assessed.

Bunn et al. (1977), attempting to analyse the response rate and survival in collected studies using combined modality treatment, found the results to be better for those receiving chemotherapy and radiotherapy (complete response rate: 23% chemotherapy alone and 37% chemotherapy plus radiotherapy). The pitfalls encountered in this approach can be appreciated as 37% of patients receiving combined modality treatment had localized disease compared with only 16% amongst the patients receiving chemotherapy alone. Combination chemotherapy alone should be the standard therapy of *extensive* small-cell carcinoma of the lung until trials can show a role for combined modality therapy in this form of the condition.

Problems for the future

The role of 'maintenance' therapy. With the attainment of high complete response rates the question of how long to continue treatment arises. Johnson et al. (1978), after their very intensive induction therapy, gave no further therapy; 14 of their 33 patients with limited disease remained relapse-free at 30 months. For those with advanced disease the relapse-free survival at two years is 40% for complete responders. Future trials will examine the role of maintenance therapy following the attainment of a complete response.

Management of the relapsed patient. Unfortunately the majority of patients achieving complete remission eventually relapse. A second complete remission may be achieved even with single agent therapy. Using an alternative regimen, Cohen et al. (1977*a*) achieved a 24% complete response rate in previously treated patients who had relapsed on the three drug regimen cyclophosphamide, methotrexate and CCNU. Many clinicians and patients would, however, be unwilling to embark on a further course of intensive chemotherapy after a relapse on primary therapy. It is in these patients that the response to new agents may be assessed by carefully controlled phase II studies.

Tumour models. Many cell lines derived from oat-cell carcinomas have now been described, and because of their APUD characteristics they are fascinating cells to study (Ohara & Okamoto 1977; Pettengill et al. 1977; Gazdar et al. 1978). Cell lines grown in tissue culture or immunosuppressed mice are being increasingly used to test new drugs or combinations. Only careful clinical trials will show whether it will be possible to translate success in the laboratory to an improved clinical response. There is perhaps insufficient communication between the clinicians and research workers and closer cooperation, particularly in providing tissue specimens, must facilitate progress. Recently Salmon et al. (1978) have developed an in vitro sensitivity test which has allowed them to predict with some accuracy which drugs a patient will respond to. Although such methods are in their infancy their use may be extended to the study of small-cell carcinoma of the lung.

CONCLUSION

Small-cell carcinoma of the lung is highly related to cigarette smoking and the failure of anti-smoking campaigns will result in a major health problem for many years to come. If present mortality rates continue, 300 000 patients will die of lung cancer in the UK during the next 10 years, 70 000 of these from small-cell carcinoma of the lung.

Median survivals of approaching one year in recent clinical trials may seem dismal, but should be viewed in the context of a seven-week median survival in the untreated. The gradual improvements in the planning and results of chemotherapy and radiotherapy in small-cell carcinoma of the bronchus remains the one encouraging feature in the management of lung cancer. A small proportion of patients with limited disease may be cured using current combined modality approaches.

Though the optimal management of small-cell carcinoma of the lung is far from clear, future trends are now becoming evident:

1. It is a distinct disease entity requiring different treatment from other types of lung cancer. Histopathology of lung cancer should therefore be reported according to the WHO or Lung Cancer Working Party classifications. The prognostic influence of subtypes of small-cell carcinoma of the lung requires further assessment in large trials.
2. Staging should probably be carried out in all patients and should include in particular screening of the liver, bone marrow, bones and brain. Initial staging will become important if it is shown that surgery or radiotherapy are an important part of therapy for pathologically staged localized disease. In the meantime, staging increases our knowledge of the natural history of small-cell carcinoma of the lung and will allow 're-staging' in patients achieving a complete remission.
3. Surgery is perhaps of little use except for solitary peripheral nodules. The role of surgery for stage I disease in pathologically staged patients has not been properly assessed and should be tested in clinical trials. Adjuvant chemotherapy should be studied in these groups.
4. Radiotherapy alone is less effective than chemotherapy both for limited or extensive disease. The dose of radiotherapy has, however, frequently been suboptimal.
5. Small-cell carcinoma of the lung is highly chemosensitive and encouraging response rates with single agents have been reported. Combination chemotherapy is preferable to single-agent therapy, the optimal number of drugs being three or four.
6. The addition of radiation therapy to effective chemotherapy has not improved survival in patients with extensive disease. The role of radiation therapy with chemotherapy in localized disease has yet to be defined though several trials on concomitant radiotherapy and chemotherapy have shown improved survival for patients with localized disease.
7. Prophylactic cranial irradiation markedly reduces the incidence of brain metastases, while not apparently improving survival.
8. All trials should be designed to achieve complete remission; prolonged survival occurs only in these patients.
9. Future trials should explore the use of new drug combinations. New regimens should include intensive induction chemotherapy to try to improve the initial complete remission rate. The use of consolidation and maintenance therapy in patients achieving complete remission will need to be explored.

10 New fractionation and dose schedules for radiotherapy must be designed and new ways of combining radiotherapy and chemotherapy devised. The combination of surgery and adjuvant chemotherapy for patients with pathologically staged minimal disease also deserves further assessment.

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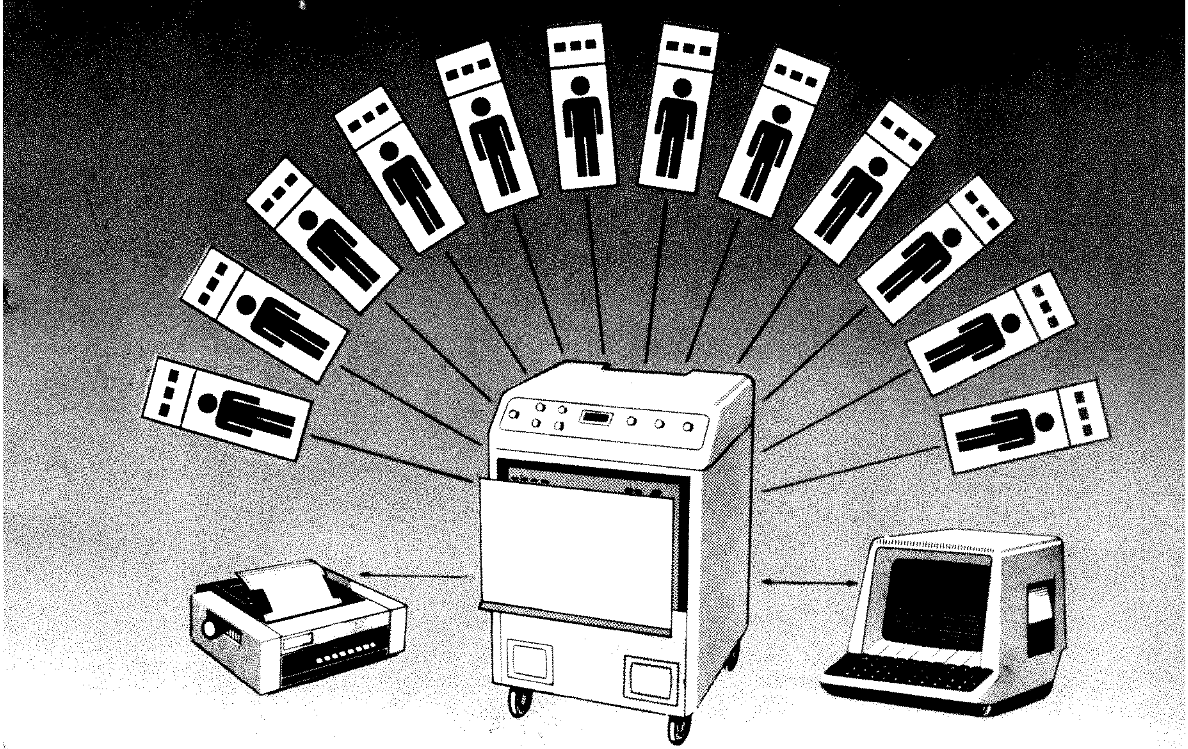

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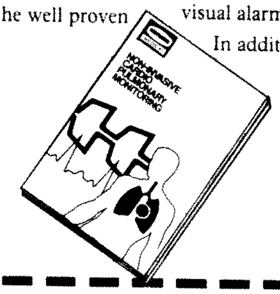

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In controlling chronic asthma, the bronchodilator is usually the first line of attack. Often it will be the only treatment required.

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In short, Bextasol inhaler allows the asthmatic to breathe and to live life to the full.

Artist's representation bronchospasm

Bronchospasm complicated by mucosal oedema and hypersecretion of mucus.

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(betamethasone valerate)

Prescribing information

Presentation

A pressurised aerosol containing a suspension of betamethasone valerate B with propellants which supplies 200 metered inhalations, each providing 100mcg of betamethasone valerate.

Dosage and administration

The recommended initial dosage in adults and children is 800mcg daily, usually as two puffs four times daily in addition to any other therapy the patient is receiving. When asthma is complicated by hyper secretion of mucus, Bextasol may not reach the mucosa in effective amounts. A short intensive course of systemic corticosteroid therapy may remedy this. Provided the asthma is fully controlled, dosage of Bextasol and ancillary drugs can often be reduced slowly over a few weeks to the minimum necessary to obtain control. Where severe asthma has required maintenance treatment with systemic corticosteroids or ACTH, these may be reduced, or even withdrawn eventually, by the equivalent of 1mg prednisolone per day at weekly to monthly intervals, but great care is necessary in case of pituitary or adrenal hypofunction. Corticosteroid withdrawal symptoms including anorexia, nausea, vomiting, muscle and joint pains may occur. Furthermore, atopic condition such as rhinitis and eczema, which were suppressed by systemic corticosteroid, may be unmasked, and require therapy.

Contra-indications

Hypersensitivity to betamethasone valerate.

Precautions

Caution should be exercised in the presence of bacterial, mycobacterial, viral or fungal infections of the respiratory tract. Hypothalamic-pituitary adrenal function recovers only gradually after systemic corticosteroid therapy depending on dosage and duration. The possibility that severe stress may precipitate acute adrenal insufficiency can remain for a year or longer. During this period it is advisable for the patient to have a reserve supply of corticosteroid tablets so that if the asthma deteriorates, or infection occurs, he can increase or reinstate systemic therapy pending instructions from his physician. In pregnant animals, administration of corticosteroids can cause foetal abnormalities. The relevance of this finding to humans has not been established.

Side effects

Some patients have reported hoarseness. Occasionally localised colonisation by *Candida albicans* occurs in the mouth and throat, and usually requires topical antifungal therapy. If the response is unsatisfactory, temporary reduction in the dosage of Bextasol often speeds resolution.

See Data Sheet for complete information.

Product Licence number: 4/0142

Basic NHS cost (exclusive of VAT): £2·90 per inhaler.

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Br. J. Dis. Chest (1979) *73*, 349

INHALED BECLOMETHASONE DIPROPIONATE IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS*

REPORT TO THE RESEARCH COMMITTEE OF THE
BRITISH THORACIC ASSOCIATION

Summary

A double-blind multi-centre study was carried out to assess the effects of beclomethasone dipropionate aerosol on the control of symptoms of asthma and on fungal colonization of the bronchi, in patients with allergic bronchopulmonary aspergillosis who had not been treated with an inhaled corticosteroid preparation for at least six months. Each of the 32 patients who completed the trial was treated with beclomethasone (100 μg four times daily) or placebo aerosol for consecutive periods of six months without alteration of the pre-study maintenance therapy. Treatment of exacerbations of asthma and of pulmonary eosinophilia was left to the discretion of the participating physicians.

The only statistically significant finding was an association between serum *Aspergillus* antibody levels and episodes of pulmonary eosinophilia diagnosed by radiography. During treatment with beclomethasone improvement occurred in ventilatory function and control of asthma, but *Aspergillus fumigatus* was detected in the sputum more frequently than during the placebo period. None of these trends attained statistical significance. Episodes of pulmonary eosinophilia were not reduced by beclomethasone and usually occurred without clinical deterioration of asthma.

INTRODUCTION

Corticosteroid treatment by inhalation is now an established and valuable treatment of chronic asthma since it is free from the systemic side-effects frequently seen in patients treated with long-term oral or parenteral corticosteroid drugs. Oropharyngeal candidiasis is a local adverse effect of inhaled corticosteroids but the mechanisms by which high concentrations of drug induce yeasts commensal in the oropharynx to become pathogenic are not understood. The local effect of inhaled corticosteroids on fungi already present in the bronchi is not known and hence it was decided to study the consequences of inhaled corticosteroids in patients with asthma complicated by pulmonary eosinophilia due to *Aspergillus fumigatus*. Patients with allergic bronchopulmonary aspergillosis are known to have a better long-term prognosis when given long-term oral prednisolone (Middleton et al. 1977) since the number of episodes of pulmonary eosinophilia is reduced. To avoid the long-term side-effects of systemic corticosteroid treatment it would be rational to replace oral treatment, wholly or in part, by an inhaled corticosteroid preparation, provided it was known that inhalation therapy did not increase fungal colonization of the bronchi and that replacement of oral by inhaled corticosteroids did not result in exacerbation of allergic aspergillosis. This study was, therefore, designed to assess the effects of inhaled beclomethasone dipropionate in patients with allergic bronchopulmonary aspergillosis. The aims of the study were: (*a*) to assess the efficacy of this treatment in the control of symptoms of asthma and (*b*) to investigate the effects of inhaled beclomethasone on fungal colonization of the bronchi.

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* This report was prepared by Dr G. K. Crompton on behalf of the sub-committee, which consisted of Dr K. M. Citron (*Chairman*), Dr G. K. Crompton (*Coordinator*), Mr G. Berry, Dr L. J. R. Milne and Dr A. Pines. Participating physicians were: Dr K. M. Citron (Wandsworth Chest Clinic, London), Dr R. A. Clark (Royal Infirmary, Sheffield), Dr G. K. Crompton (Northern General Hospital, Edinburgh), Dr D. Davies (City Hospital, Nottingham), Dr A. C. Douglas (City Hospital, Edinburgh), Dr J. A. R. Friend (City Hospital, Aberdeen), Dr A. T. Hendry (Royal National Hospital, Bournemouth), Dr E. Hills (Tindal General Hospital, Aylesbury), Dr S. Lal (Bury General Hospital, Bury), Dr K. Lim (Chest Clinic, Barnet), Professor J. Pepys (Brompton Hospital, London), Dr G. K. Ray (Royal Infirmary, Hull), Dr J. D. Stevens (Chest Clinic, Rotherham) and Dr R. H. Townsend (Royal Infirmary, Sheffield).

Patients and Methods

For the purposes of this study allergic bronchopulmonary aspergillosis was defined as a condition in which patients with asthma develop radiographic pulmonary shadows associated with blood eosinophilia (absolute count in excess of 500×10^6/litre) and have precipitating antibodies to *A. fumigatus* in their serum and a positive immediate prick skin test to an extract of *A. fumigatus*.

Patients were eligible for study if they fulfilled these criteria and had not been treated with an inhaled corticosteroid preparation for at least six months, provided they were capable of using a pressure-packed aerosol correctly and were willing to complete diary cards daily throughout the duration of the study. The patients who produced sputum were required to make 24-hour collections. Maintenance therapy was kept constant throughout the study except for the treatment of exacerbations of asthma or pulmonary eosinophilia which was left to the discretion of the participating physicians.

The study was a multi-centre, double-blind randomly allocated six-month cross-over comparison of beclomethasone aerosol 100 μg four times daily with placebo aerosol.

Investigations

Sputum. Three consecutive 24-hour samples of sputum were collected on entry and thereafter one 24-hour volume at the end of each month. All sputum specimens were sent for examination to Dr L. J. R. Milne, Mycology Unit, Western General Hospital, Edinburgh.

In the laboratory the entire volume of each 24-hour collection was treated with a pancreatic enzyme preparation and the resulting homogenate was centrifuged and the supernatant discarded. The sediment *in toto* was cultured for *A. fumigatus* after a small quantity had been removed for microscopy. Two smears were examined for the presence of the characteristic hyphae of *Aspergillus*. One was prepared by adding a sample of the sediment to a drop of potassium hydroxide on a slide and viewed under dark-ground illumination. A second preparation was examined by conventional light microscopy after staining with methenamine silver nitrate (Grocott 1955).

Blood. Serum for antibodies to *A. fumigatus* was collected on entry and every two months during the study and sent to Professor J. Pepys, Department of Clinical Immunology, Cardiothoracic Institute, London. *Aspergillus* precipitating antibodies were determined. In addition levels of specific IgG and IgE antibodies were measured using the semiquantitative enzyme-linked immunosorbent assay (ELISA) (Sepulveda et al. 1979).

Chest radiographs. Radiographs were made on entry and at every second month and despatched to the study coordinator. Additional chest radiographs were also taken whenever the participating physician thought the patient was suffering an exacerbation of pulmonary eosinophilia. The radiographs were read independently by two experienced observers and any new pulmonary opacity was recorded as evidence of an exacerbation of pulmonary eosinophilia.

Records

Diary cards. The patients completed diary cards each day during the study and recorded their symptoms of asthma that day by marking a 50 mm line labelled VERY BAD at one end and PERFECT at the other. They also indicated the volume of sputum in a similar way by marking a 50 mm line labelled NONE at one end and A LOT at the other. The regularity of study aerosol administration and any changes in maintenance therapy were also recorded. Diary cards were collected by the participating physician every month.

Physician assessment card. At the end of each month the physicians made their own assessment of the patient's progress and graded the patients as A = the same as usual, B = better than usual or C = worse than usual. If a C assessment was made the physicians were asked to state whether they thought the patient was suffering from an exacerbation of pulmonary eosinophilia. The physician's monthly assessment also included measurement of the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC). Any changes of treatment were also recorded. Special exacerbation forms were completed when it was considered that an episode of pulmonary eosinophilia had occurred.

Statistical methods

To avoid carry-over effects of treatment, data collected during the first month of each study period were not analysed. The results presented are, therefore, from analyses of data from Months 2 to 6 inclusive and 8 to 12 inclusive unless stated otherwise.

The variables recorded on a continuous scale—FEV, FVC, chest and sputum scores—were analysed as follows. The mean values during the active and placebo periods were calculated for each patient and the difference between these two mean values taken as a measure of the treatment effect. The differences were calculated so that a positive value indicates better results with active treatment than with placebo and *vice versa*. For all of the variables there were one or two of the differences which were markedly different from the others and, for this reason, the significance was established using Wilcoxon's non-parametric signed rank sum test (Armitage 1971). The serological results were analysed in the same way.

For the variables such as treatment changes and exacerbations which were recorded as events, the number of events occurring in each treatment period was counted for each patient. The significance was assessed by comparing the number of patients who had more events in the active period with the number who had more in the placebo period (sign test; Armitage 1971).

The significance of the association between the serological results and exacerbations was assessed by the calculation of a χ^2 statistic for a trend in proportions (Armitage 1971).

RESULTS

Thirty-six patients were entered into the study from 14 centres and four were withdrawn because of lack of cooperation. Data were available for analysis from 32 patients.

Ventilatory functions tests and diary card scores

The mean FEV_1 during the placebo period was 1.98 litres (range 0.82–4.40 litres) and the mean FVC was 3.29 litres (range 1.23–6.7 litres). Fig. 1 shows the results of changes in FEV_1, FVC, asthma symptom scores and sputum scores plotted for each patient so that a positive value indicates that the index measured was better during the active treatment period and, conversely, a negative value below the line indicates that

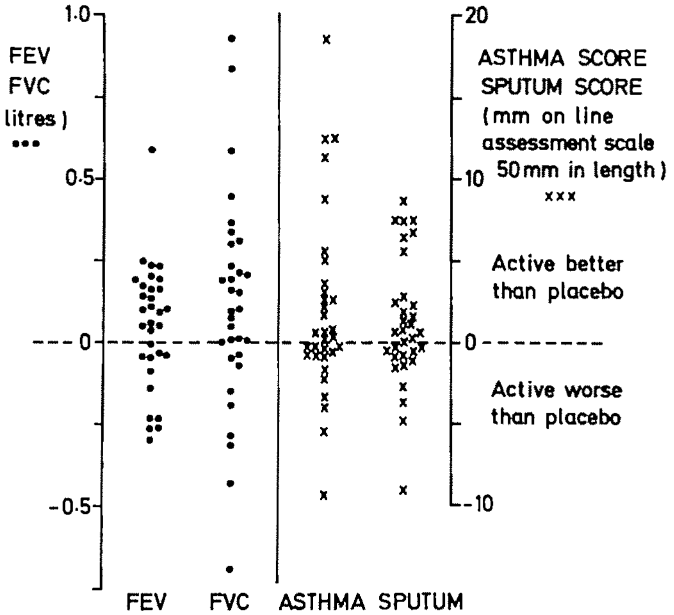

Fig. 1. Changes in FEV, FVC, asthma symptom scores and sputum scores plotted for each patient so that a positive value indicates improvement during active treatment and a negative value improvement during placebo treatment

placebo treatment was better than the active therapy. The mean differences and standard errors of the mean differences are as follows: FEV_1 0.06 ± 0.03, FVC 0.11 ± 0.05, asthma score 1.8 ± 0.8 and sputum score 0.6 ± 0.7. For all of these the active treatment was better than placebo but for each of the four indices the difference was significant only at the 10% level (signed rank sum test) but the difference did not reach significance by conventional statistical standards.

Treatment changes

Twenty-two patients were taking prednisolone regularly as maintenance therapy and in these a treatment change was defined as an increase in the dose. In the ten patients who were not taking this drug regularly a treatment change represents a course of treatment with prednisolone. Thirty patients were not on long-term antibiotic treatment and in these any antibiotic therapy was regarded as a treatment change. A treatment change in the two patients on long-term therapy was defined as a change of antibiotic. Table I shows the prednisolone and antibiotic treatment changes made. The total number of prednisolone treatment changes was 26, 18 during the placebo and eight during the active periods. The lower part of the table shows the number of patients who had treatment changes. Thirteen patients had change of prednisolone, nine had more changes during the placebo period, two had more changes in the active period ($P = 0.07$) and for two there was no difference. The antibiotic treatment changes were almost equally divided between the two treatment periods.

Table I. Treatment changes

Treatment changes	*Prednisolone*	*Antibiotic*
No. during active treatment	8	25
No. during placebo period	18	25
No. of *patients* involved	13	20
Treatment changes more frequent during active treatment	2	9
Treatment changes more frequent during placebo period	9	8
Equal changes during active and placebo periods	2	3

Exacerbations

Exacerbations were defined as clinical exacerbations when the participating physician assessed the patient as 'worse than usual' but there was no radiological evidence to suggest an exacerbation of pulmonary eosinophilia. Exacerbations detected by the appearance of a new radiographic abnormality were classified as radiographic exacerbations, whether or not these were accompanied by a clinical exacerbation. There were seven clinical exacerbations during the active period and 14 during the placebo period. This difference is not statistically significant ($P=0.11$). There were 18 radiographic exacerbations during the active period of treatment compared with 11 during placebo; again this difference could be due to chance ($P=0.58$).

Mycology

The mycological findings are of diagnostic significance only when the isolation of *A. fumigatus* is accompanied by the observation of the characteristic hyphae on microscopy, otherwise the fungal colonies may have arisen exclusively from spore sources and thus be of no clinical relevance. For example, isolation of *A. fumigatus* was common during the study and in one 24-hour collection no fungal elements were observed although 1000 colonies were obtained on culture.

The total number of colonies varied greatly between patients and also between specimens from the same patient as is characteristic of allergic bronchopulmonary aspergillosis (Milne & Crompton 1979). For example, the numbers of colonies in the specimens found to contain fungal hyphae on microscopy ranged from 6 to 380 000 in sputum volumes of 0.1 and 6.6 ml respectively. Fourteen of the 29 patients with sputum had hyphae observed in their sputum at some time during the 12-month period of the study. During the periods analysed fungal hyphae were observed on 25 occasions during active therapy and on 16 during placebo treatment. This difference may be due to chance ($P=0.58$).

Serology

Aspergillus precipitating antibody was used as a criterion for inclusion in the study. However, the precipitin test is unsatisfactory as a quantitative technique. Therefore,

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A. fumigatus specific IgG and IgE were measured by the ELISA technique. The values for these antibodies were analysed during the same time periods as FEV_1 and FVC. Fig. 2 shows the differences between the active and placebo periods and for both values there is no statistical significance (IgG mean differences 0.02 ± 0.04, IgE 0.005 ± 0.010). However, there was an association between the antibody levels and radiographic exacerbations (Table II). The four patients with more exacerbations in the placebo period all produced more antibody during this time, whilst six out of the eight patients with more exacerbations in the active treatment period also produced more antibody in this period.

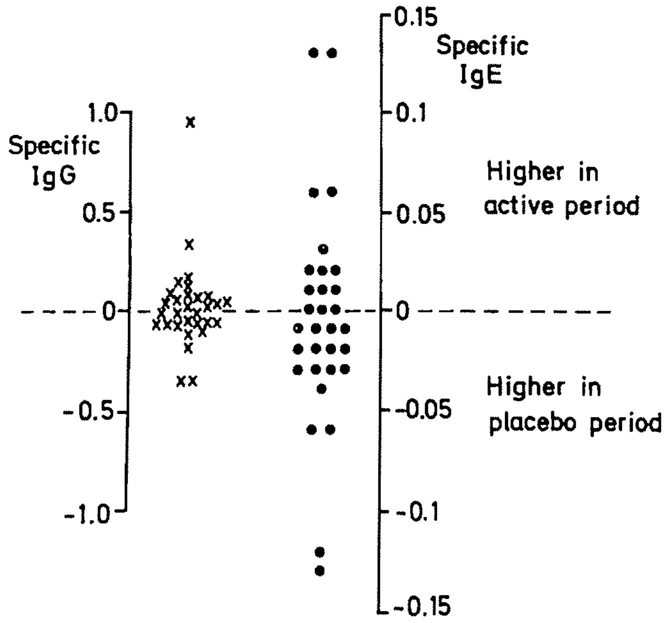

Fig. 2. A. fumigatus specific IgG and IgE values plotted for each patient so that a positive value indicates higher levels during active treatment and a negative value indicates high level during placebo treatment

Table II. Serology and radiographic exacerbations

Radiographic exacerbations	*Higher IgG antibody on*		*Higher IgE antibody on*	
	Placebo	Beclomethasone*	Placebo	Beclomethasone*
More radiographic exacerbations during placebo ($n = 4$)	4	0	4	0
Equal exacerbations on both regimens ($n = 19$)	9	10	11	8
More radiographic exacerbations on beclomethasone ($n = 8$)	2	6	2	6

* Includes the few patients whose antibody levels were the same with placebo as with beclomethasone. No serological data were available for one patient.

The other patients, 18 of whom had no radiographic exacerbations, produced more antibody in the active and placebo periods in approximately equal proportions. The association was significant for both IgG and IgE ($P < 0.05$).

DISCUSSION

This study was designed to assess the effect of beclomethasone aerosol therapy on the control of symptoms of asthma and the results suggest that patients were better during the active treatment period since they required fewer courses of treatment with prednisolone than they did in the placebo period. Also there were fewer clinical exacerbations during active treatment although the difference between clinical exacerbations in the two treatment periods failed to reach statistical significance. Clinical exacerbations without associated radiological change can be regarded as simple increases in the severity of asthma. As a group, therefore, the control of symptoms of asthma was improved by the addition of beclomethasone treatment to the maintenance therapy.

Although the control of asthma seemed better during treatment with beclomethasone, more radiographic abnormalities were detected during this period. Eighteen new radiographic shadows appeared during beclomethasone treatment and 11 in the placebo period. Although this difference does not achieve statistical significance it is of some concern since in the management of patients with allergic bronchopulmonary aspergillosis it may be important to suppress episodes of pulmonary eosinophilia if the prognosis is to be improved. Each pulmonary abnormality must be regarded as a potential cause of bronchiectasis, the major complication of this disease. Two-thirds (19) of the pulmonary shadows occurred at times when the participating physicians assessed the clinical state of the patient as 'same as usual' or 'better than usual'. On only seven occasions was a change of treatment made at a time when a radiographic abnormality developed. Twenty-two episodes of pulmonary eosinophilia diagnosed radiographically were therefore untreated except by the patient's normal maintenance therapy. It is clear from these findings that potentially destructive episodes of pulmonary eosinophilia can and do occur without clinical deterioration of asthma and it is conceivable that treatment with beclomethasone may control symptoms of asthma without reducing episodes of pulmonary eosinophilia. Hence regular radiographic examination of patients suffering from allergic bronchopulmonary aspergillosis is necessary if exacerbations of bronchopulmonary eosinophilia are to be detected, no matter how well the symptoms of asthma appear to be controlled. This study suggests that, although asthmatic symptoms may be better controlled by beclomethasone, clinically undetectable episodes of pulmonary eosinophilia may be increased.

We found a statistically significant association between *A. fumigatus* specific IgG and IgE antibody levels and radiographically diagnosed exacerbations of pulmonary eosinophilia. This is the first time that this association has been observed. Further work is required to establish whether this test is of clinical value in identifying patients who may be having clinically undetectable episodes of pulmonary eosinophilia.

The mycological findings also support the hypothesis that the inhalation of beclomethasone dipropionate by patients with allergic bronchopulmonary aspergillosis does not suppress the activity of *A. fumigatus* and could possibly enhance it, since more fungal hyphae were seen on microscopy of sputum specimens submitted during the active treatment period. As with the radiographic exacerbations, however, this mycological finding can only be regarded as suggestive since differences between the active and placebo treatment periods did not reach statistical significance.

It can be concluded from the results of this multi-centre double-blind study that beclomethasone dipropionate by inhalation improved the overall control of the asthmatic symptoms of the 32 patients with allergic bronchopulmonary aspergillosis, 22 of whom were taking prednisolone as maintenance therapy. Episodes of pulmonary eosinophilia diagnosed by the appearance of a new pulmonary shadow on the chest radiograph, frequently without an associated deterioration of asthmatic symptoms, were not prevented by beclomethasone treatment and there is a hint that they may even be increased by this form of corticosteroid therapy.

ACKNOWLEDGEMENTS

We thank Professor J. Pepys, Dr R. Sepulveda and Miss J. Mitchell for the specific *A. fumigatus* serology studies.

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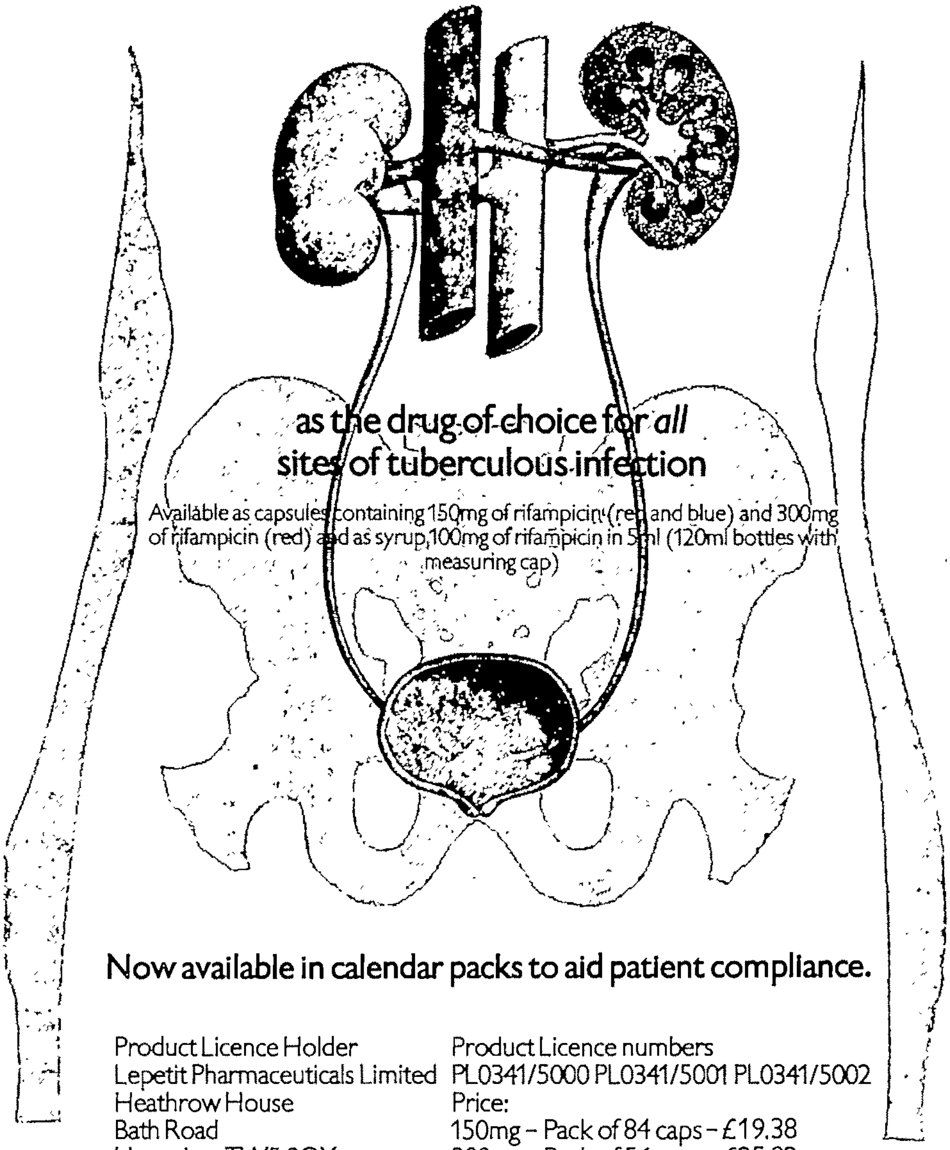

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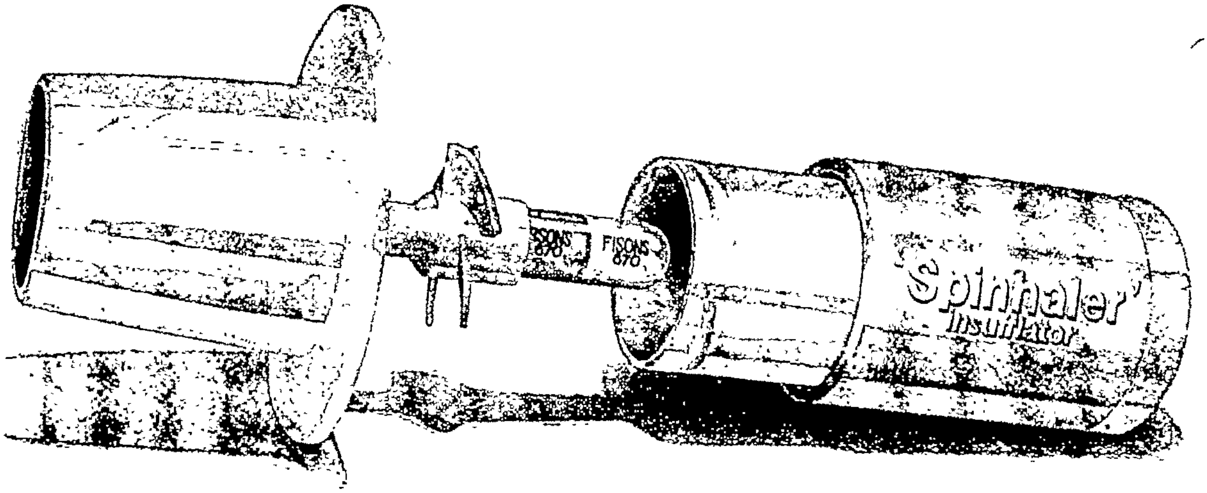

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DIURNAL RHYTHMS IN AIRWAY OBSTRUCTION

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Summary

Diurnal patterns of variation in peak expiratory flow rate were studied in patients with all types of airway obstruction. Most regular patterns fall into one of two types: morning dip (M) with the lowest reading in the morning and (P) or double dip with the lowest readings morning and evening. Regular patterns were most frequently seen in asthmatics, but occurred also in bronchitis, particularly those with a history of wheeze. Treatment with bronchodilators reduces the prevalence of all regular patterns but does not abolish them. M pattern is characteristic of asthma but P pattern is the most frequent regular pattern seen in bronchitis. Amplitude of variation is greater in asthmatics than in simple bronchitics. It is reduced by about 20% with bronchodilators. Random observation of magnitude of response of peak flow rate to a bronchodilator is not a good indicator of amplitude of variation over the day. Because of the occurrence of a peak pattern in many patients the magnitude of diurnal variation may be underestimated by twice-daily peak flow rate readings. Treatment with corticosteroids does not appear strongly to influence either characteristic patterns or amplitude of variation.

INTRODUCTION

Patients with airway obstruction commonly complain that their wheeze varies in severity from time to time, often consistently at certain times of the 24 hours. This was first documented in 1960 (Lewinsohn et al.), but little is known of the prevalence and nature of such variation in asthmatics and in other patients with airway obstruction (Turner-Warwick 1977). A nomenclature is proposed to describe the different characteristic patterns seen in such patients when studying their peak expiratory flow rates four-hourly. The pattern and amplitude of variation seen in different groups of patients are described. The results here include those of 295 patients presented in a preliminary report (Connolly 1977).

Patients and Methods

Patients attending two district general hospitals between 1973 and 1977 were studied. Of 350 patients, the majority (328) were in-patients and 22 were studied at home. In-patients were unselected from emergency and other admissions for assessment and treatment of airway obstruction. They were divided into four diagnostic groups:

1. *Emphysema*: history of predominant breathlessness and characteristic chest radiograph appearances of low flat diaphragms, retrosternal radiotranslucency and comparison with 'marker vessels' (Simon 1971).

2. *Bronchitis*: Medical Research Council criteria (1965).

3. *Asthma*: history of reversible wheeze confirmed by improvement of at least 20% in peak flow or FEV_1 after bronchodilator, to reach 75% of predicted normal; together with blood eosinophilia of greater than $250/mm^3$.

4. *Wheezy chronic bronchitis*: see below.

Where there was doubt between bronchitis and emphysema or where they were thought to coexist, the diagnosis was recorded as bronchitis. Where there was doubt between bronchitis and asthma the subject was placed in a fourth group. If the patient has the symptoms of bronchitis and both criteria for asthma were also present a diagnosis of asthma was made, but where only one criterion for asthma was present the patient was included in the fourth group. In doubtful cases, particularly where the history suggested that the wheeze preceded the symptoms of bronchitis, other criteria were used in the assessment. A good history of reversibility which was not supported by ventilation studies, demonstration of spirometric improvement but not to 75% of predicted normal, sputum eosinophilia and good corticosteroid response all favoured asthma. Patients in the fourth group all had chronic bronchitis by Medical Research Council criteria (1965), but also a predominant history of wheeze and are referred to as wheezy chronic bronchitics.

Except for the ten who received no treatment, all patients were treated with bronchodilators of the isoprenaline group by inhalation at intervals of four hours from 0600 hours. Peak flow rate was recorded four-hourly, starting at different times, 0600 hours and 0800 hours, in two groups. In the 0600 hours group peak flow rate was recorded immediately before treatment and in the 0800 hours group the first recording was at 0800 hours, which was mid-way between the regular doses. Some patients also had theophylline derivatives. Patients on corticosteroids were included and where peak flow readings were available before and after starting corticosteroid administration both were analysed. The analysis of the established patterns in patients was based on records made at least four days after starting corticosteroid administration and at least 24 hours after the plateau of improvement had been achieved.

Throughout this paper the practice of regarding a result as statistically significant if the probability is less than 5% has been adopted, and 'significant' is to be regarded as meaning this unless otherwise stated. Student's t-test was used, but where the F ratio indicated disparity in the variance Welsh's test was employed. For qualitative data the normal tests were applied or in the case of small expectations the exact probability was calculated.

Nomenclature

The pattern and amplitude of the variation in peak flow rate over a waking day (or any waking period) are described by a letter and number respectively:

Pattern (*Fig. 1*)

Four simple patterns are possible:

1. Morning dip (m), where the lowest reading is in the morning.
2. Evening dip (e), where the lowest reading is in the evening.
3. Peak (p), where the highest reading is in the middle of the day with low waking and retiring figures.
4. Trough (t), where the lowest reading is in the middle of the day.

Those not showing one of these patterns are described by x.

In peak or trough patterns the short limb must be 20% or more of the long limb, otherwise m or e is recorded. In peak patterns the position of the longer limb is described by subscript m or e as appropriate. Thus p_m refers to a day showing a peak pattern but with the lowest reading in the morning.

Amplitude

The magnitude of variation (amplitude of variation) is measured as the difference between the lowest and the highest peak flow rate of the day, expressed as a percentage of the highest.

A combination of one letter and one figure describes the events of one day, e.g. m 25 is the rhythm on a day where there is a morning dip and a total amplitude or variation of 25%.

The events of a longer period are similarly described. An upper case letter is used to describe an established pattern which must occur on at least 70% of four or more consecutive days (Fig. 2a). If the lowest figure is in the morning on at least 70% of days M is recorded even if a peak pattern is shown on some of those days (Fig. 2b). In peak patterns, if morning or evening readings are lowest on at least 70% of days the subscript M or E is used (Fig. 2c).

Amplitude of variation is measured as the mean magnitude of variation of all the days of a period, including those which do not show the characteristic pattern of that period. Thus an established rhythm over a period of days might be recorded as P25, to indicate a peak pattern on at least 70% of days with a mean amplitude of variation of 25%. P_M25 would be used if the morning fall predominated on 70% of days.

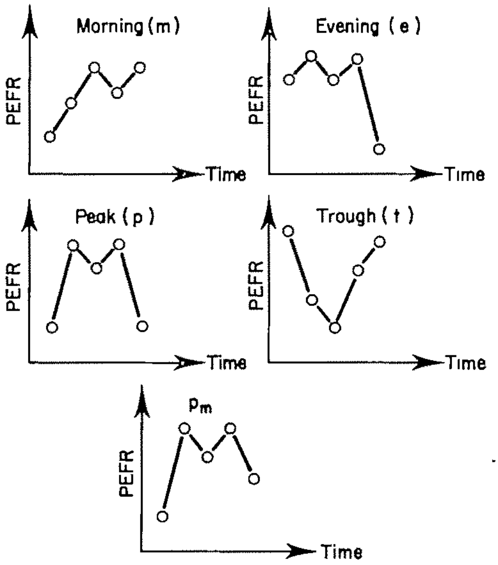

Fig. 1. Type of pattern seen on a single day's observation

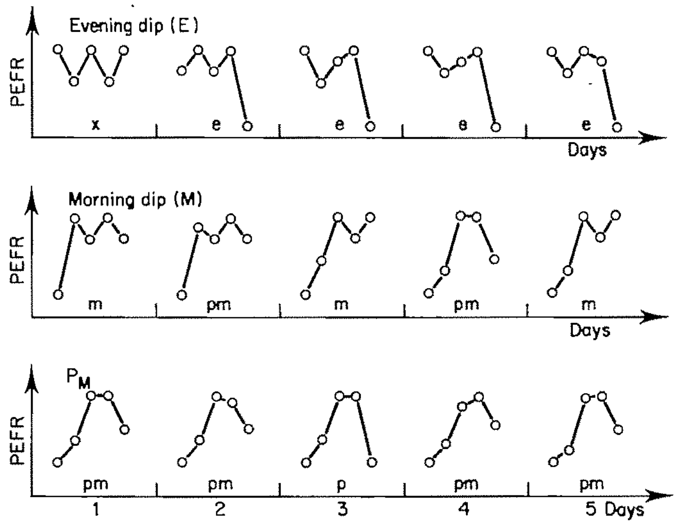

Fig. 2. Characteristic pattern seen over an observation period of five days

RESULTS

General

The 350 patients of mean age 56 years (range 10–81) were distributed between the diagnosis as in Table I, which also shows the mean severity as measured by mean peak expiratory flow rate for the observation period of not less than four days. Only in the bronchitics were the women significantly younger than the men, while the peak flow rate was significantly lower in women in all diagnostic groups except emphysema. Age and sex have not been considered further except where stated in the text, as differences in pattern and amplitude of variation associated with age and sex are consistent with excess of the (younger) asthmatics amongst the women.

Table I. Distribution of subjects ($n=350$) by diagnosis with age and mean peak flow rate

Diagnosis	*Sex*	*No.*	*Mean age* (years)	*Mean PEFR* (litres/min)
Asthma	M	44	48	236
($n=115$)	F	71	45	192
Wheezy chronic bronchitis	M	50	59	178
($n=91$)	F	41	59	144
Bronchitis	M	90	63	182
($n=118$)	F	28	58	127
Emphysema	M	19	62	135
($n=26$)	F	7	56	97

A pattern was seen in 49.5% of patients, distributed as in Table II. A characteristic pattern occurred most often in asthma, less often in chronic wheezy bronchitis and least in bronchitis. In emphysema the pattern was as in the mixed group. In asthma and wheezy chronic bronchitis, men showed a P pattern more often (34%) and an M pattern less often (24%) than women (P 23% and M 34%).

Table II. Prevalance of the characteristic patterns within the diagnostic groups ($n=350$)

Diagnosis	*No.*	*Percentage showing pattern*				
		Morning	Peak	Evening	Trough	No pattern
Asthma	115	36	30	1	1	31
Wheezy chronic bronchitis	91	19	26	2	—	53
Bronchitis	118	9	21	1	—	69
Emphysema	26	8	42	4	—	46

The proportion of morning and peak patterns amongst those showing any regular pattern is shown in Table III. It will be seen there is a clear trend for the morning pattern to decrease and for the peak pattern to increase from asthma through wheezy

Table III. Type of pattern amongst those showing a characteristic pattern ($n = 173$) within each diagnostic group

Diagnosis	*No.*	*Percentage showing pattern*			
		M	($M+P_M$)	P	E
Asthma	79	53	(73)	44	1
Wheezy chronic bronchitis	43	40	(47)	55	5
Bronchitis	37	30	(41)	68	3
Emphysema	14	14	(21)	79	7

chronic bronchitis to bronchitis, with emphysema showing a peak pattern most frequently. If all patients on whom the morning reading is consistently lowest ($M+P_M$) are taken, the predominence of the lowest first morning reading in asthma is further emphasized.

The amplitude of variation was largest in asthma, smaller in wheezy chronic bronchitis and smallest in bronchitis. It is rather greater in emphysema than in bronchitis (Table IV). The means of the amplitude of variation in asthma and in wheezy chronic bronchitis are statistically significantly different from the mean in bronchitis.

Table IV. Mean amplitude of variation for each diagnosis for all patients ($n = 350$) and according to timing of morning test of those treated by bronchodilators in hospital

Diagnosis	*All*		*0600 hours group*		*0800 hours group*	
	No.	Mean	No.	Mean	No.	Mean
Asthma	115	29	39	33	65	27
Wheezy chronic bronchitis	91	27	29	31	54	26
Bronchitis	118	23	32	26	82	22
Emphysema	26	25	7	30	18	23

Time

A pattern was seen in more of those studied from 0600 hours (68%) than in those studied from 0800 hours (37%). The difference though present in both asthma and wheezy chronic bronchitis was more marked in the latter ($P < 0.001$) than asthma ($P < 0.05$) (Table V). In the 0600 hours group wheezy chronic bronchitics closely resembled asthmatics in having a significantly higher proportion with pattern than bronchitics; but in the 0800 hours group the two groups of bronchitics could not be separated, the asthmatics having a significantly higher incidence of pattern than either ($P < 0.01$). These differences were not due to age or sex, as the mean age was similar in the two time groups and the proportion of females (who show a pattern somewhat more often) was lower in the 0600 hours group than in the 0800 hours group.

The mean amplitude of variation was 24.45% in the 0800 hours group and 29.4% in

Table V. Pattern in the different diagnostic groups ($n = 326$) according to timing of the first morning test

Pattern	*Asthma*		*Wheezy chronic bronchitis*		*Bronchitis*		*Emphysema*	
	0600 hours group ($n=39$)	0800 hours group ($n=65$)	0600 hours group ($n=29$)	0800 hours group ($n=54$)	0600 hours group ($n=32$)	0800 hours group ($n=82$)	0600 hours group ($n=7$)	0800 hours group ($n=18$)
Morning	20	19	8	7	4	6	—	2
Evening	—	1	—	1	—	1	—	1
Peak	11	20	15	7	11	12	5	5
Trough	—	1	—	—	—	—	—	—
No pattern	8	24	6	39	17	63	2	10
Any pattern	79%	63%	79%	28%	47%	23%	71%	44%

the 0600 hours group. This difference is highly statistically significant ($P < 0.001$). The amplitude of variation for the different diagnosis in the 0600 hours group and 0800 hours group is shown in Table IV.

Amplitude of variation and pattern

The relationship between amplitude of variation and the various patterns is shown in Table VI. In the 0800 hours group amplitude of variation was greatest amongst those showing M pattern, lower in those showing P pattern and least amongst those showing no pattern (X); whereas in the 0600 hours group the amplitude of variation of the M and P group were similar. Amplitude in the M group was significantly different from that in those showing no characteristic pattern at both 0600 hours and 0800 hours, and P group significantly different from them at 0600 hours only.

Table VI. Mean amplitude according to pattern and timing of first morning test of those treated with bronchodilators ($n = 321$)

Pattern	*0600 hours group*		*0800 hours group*	
	No.	Mean amplitude	No.	Mean amplitude
Morning	32	33	34	28
Peak	42	33	44	25
No pattern	33	24	136	23

Eosinophilia

Particularly as there was some doubt about the diagnostic group of some patients, the relationship with pattern and amplitude with eosinophilia was looked at independently of the diagnosis. There was a direct and significant relationship between amplitude of variation and eosinophil count (Table VII). There was increase in the proportion of

Table VII. Mean amplitude of variation and occurrence of pattern according to eosinophil count in blood ($n = 275$)

Eosinophil count (/mm^3)	*No.*	*Mean amplitude*	*Percentage showing pattern*		
			Morning	Peak	No pattern
Less than 200*	172	24	14	28	56
200–400	32	27	22	34	37
400–800	45	28	35	27	35
Over 800	26	32	38	31	31

* Including 'normal differential'.

M pattern with increasing eosinophilia, there is a suggestion that P pattern may be associated with moderate eosinophilia (count 200–400). A characteristic pattern occurred less often in those without eosinophilia in both the 0600 hours group ($P < 0.05$) and the 0800 hours group ($P < 0.005$).

Corticosteroids

There was a small but significant association between increasing amplitude of variation and increasing response to corticosteroids. Where patients were studied before and after the administration of corticosteroids, this had little effect on the prevelance of characteristic patterns, though several patients changed from P to M pattern and *vice versa*. There was no difference in amplitude of variation, though this may be because some of the patients were studied too early after the start of corticosteroid therapy for a difference to develop.

Atopic state

Amplitude or pattern were not related to atopic state as judged by skin tests to common allergens. In particular, the morning dip pattern was not related to hypersensitivity to dust mite.

Reversibility with bronchodilators recorded previously

There was no relationship between the prevelence of the characteristic patterns and the response to bronchodilators recorded previously in the laboratory or the out-patient clinic. There was only a poor relationship between amplitude of variation and response to bronchodilators. Those who improved by less than 10% did show a lower amplitude of variation but this only reached statistical significance in the sub-group of bronchitics who showed no characteristic pattern—the patients with the smallest mean amplitude of all.

DISCUSSION

The description of patterns is necessarily arbitrary but the four simple patterns suggested best represent events from the patient's point of view. Patients usually complain of being worse either in the morning (m) or the evening (e), or both (p), and occasionally at mid-day (t). Other patterns are difficult to define and are usually secondary to a clear extrinsic factor. Ideally patients should be observed for at least one week to establish patterns, so allowing for extrinsic factors at home or at work. In practice the presence of any pattern becomes apparent in four or five days, particularly in hospital.

Amplitude of variation is measured as the difference between the highest and lowest peak flow of the day expressed as a percentage of the highest. Consequently, although the absolute difference is the same, a certain amplitude of variation would be recorded as higher in those with a low flow than in those with a greater one. The variability of peak flow recording is a relatively small proportion of the reading in the normal range, but a relatively high proportion in those with low peak flow, in whom the amplitude of variation could be exaggerated. This could account for the relatively high mean amplitude of variation in patients with bronchitis and emphysema without a history of wheeze, as these had a lower mean peak flow rate than the rest of the population studied. The expression of amplitude of variation as a percentage of predicted peak flow rate would have reduced the potential for this error but was rejected because it does not reflect what is happening in the patient. An amplitude of variation of 20 litres per minute in a patient with a peak flow of 100 litres per minute, might be recorded as an amplitude of only 4% if the predicted peak flow were used. Thus the use of amplitude of variation as a proportion of the predicted recording would tend to minimize the actual changes in the severely affected subject.

As these patients had symptoms and were studied in a general hospital it was not practicable to observe most of them without treatment for four or more days, the period required by definition to identify a pattern. The two different times of measurement of peak flow rate with respect to treatment each have advantages and disadvantages. Where an attempt was made to record peak flow uninfluenced by medication (the 0600 hours group), not only was modification of the pattern by treatment less likely to occur, but also the time of the first reading of the day at 0600 hours was, of course, better than 0800 hours for recording morning dip. However, at 0600 hours the effects of prior treatment is likely to be very much less than at other times of the day because the interval since treatment is approximately eight hours rather than four. A morning dip might be produced at 0600 hours entirely by waning of the response to treatment which is present at other times. In the 0800 hours group the interval between peak flow rate measurements and bronchodilator administration is always the same at two hours, so any pattern is more likely to be modified by treatment, but consistently so at all times. It could also be argued that any pattern which is not easily suppressed by treatment is both of great fundamental interest and the most important from the patient's point of view. As anticipated the proportion of patients showing a morning dip is higher in the 0600 hours group, but many asthmatics did show M pattern in the 0800 hour group. Morning dip was a feature of asthmatics. If one included all those with a P pattern who had a predominant morning dip, then the predominance of patients with M pattern was increased. P pattern, on the other hand, particularly if one ignored those with morning predominance, was a particular feature of patients with wheezy chronic bronchitis. The predominance of M pattern in those with high eosinophilia and the direct relationship between eosinophilia and amplitude of variation are further confirmation that variation is characteristic of asthmatics.

The failure to demonstrate a relationship between morning dip and house dust hypersensitivity in patients in hospital must be seen in the context of the low hospital population of mites. Since a morning dip is observed irrespective of skin test pattern house dust hypersensitivity is unlikely to be an important cause of the morning dip. Amongst the few who recorded their peak flows at home in this study were both asthmatics with house dust mite hypersensitivity who had no morning dip and those without such hypersensitivity who had an M pattern. Further recordings at home are required, but the failure so far to demonstrate a relationship between the recurrence of house dust mite hypersensitivity and M pattern suggests that this pattern is indeed an asthmatic feature unrelated to any particular allergen.

Patients classified as suffering wheezy chronic bronchitis must represent several types of airway obstruction. A proportion may be older asthmatics whose reversibility of airway narrowing has waned, but the majority with chronic airway obstruction are bronchitics by the MRC criteria. Nevertheless, they do represent a group difficult to diagnose and manage. The pattern of peak flow reflects the frequent complaint of these patients that they are worse on getting up and going to bed. This may well be due to sputum retention morning and evening (Cochrane et al. 1977), perhaps superimposed on an asthmatic tendency to morning dip. From the practical point of view, recognition of the fact that these patients are much better at mid-day than in either the morning or the evening makes twice daily observations of peak flow little better than daily observations at a fixed time. Single measurements of reversibility of airway narrowing are not good predictors of the magnitude of amplitude of variation, so response to bronchodilators is difficult to assess in these patients without four-hourly peak flow recordings for a number of days.

The problems in the definition of amplitude of variation make it difficult to compare it with severity of obstruction. In fact, there was no relationship between severity of obstruction as assessed by peak flow rate and amplitude of variation as defined here, while there was a direct relationship between peak flow rate and numerical amplitude of variation ($r=0.86$) . Although some patients in relative remission do have a large amplitude of variation even when expressed as a percentage, the work of Clark (Cochrane & Clark 1975; Clark & Heitzel 1977) suggests that amplitude of variation is an index of clinical instability; a patient with a large amplitude of variation is probably either getting better or getting worse. For example, this was seen in a highly significant correlation between the magnitude of corticosteroid response and the magnitude of the amplitude of variation in the first two days after starting corticosteroid therapy (Connolly, unpublished).

Further work is required to establish the stability of characteristic patterns and the effect of corticosteroids on the pattern and amplitude of variation. In 59 patients of this study in whom observations where made on two separate occasions only nine showed a pattern on one occasion and not on the other, while seven showed change from M pattern to P pattern or *vice versa*. After administration of corticosteroids no change was observed in the amplitude of variation. It is possible that the minimum period of four days before recalculation of amplitude of variation and pattern could start was not long enough. It is proposed to study patients at home at intervals of some months to establish whether patterns do, in fact, vary and whether they are influenced by corticosteroids or not.

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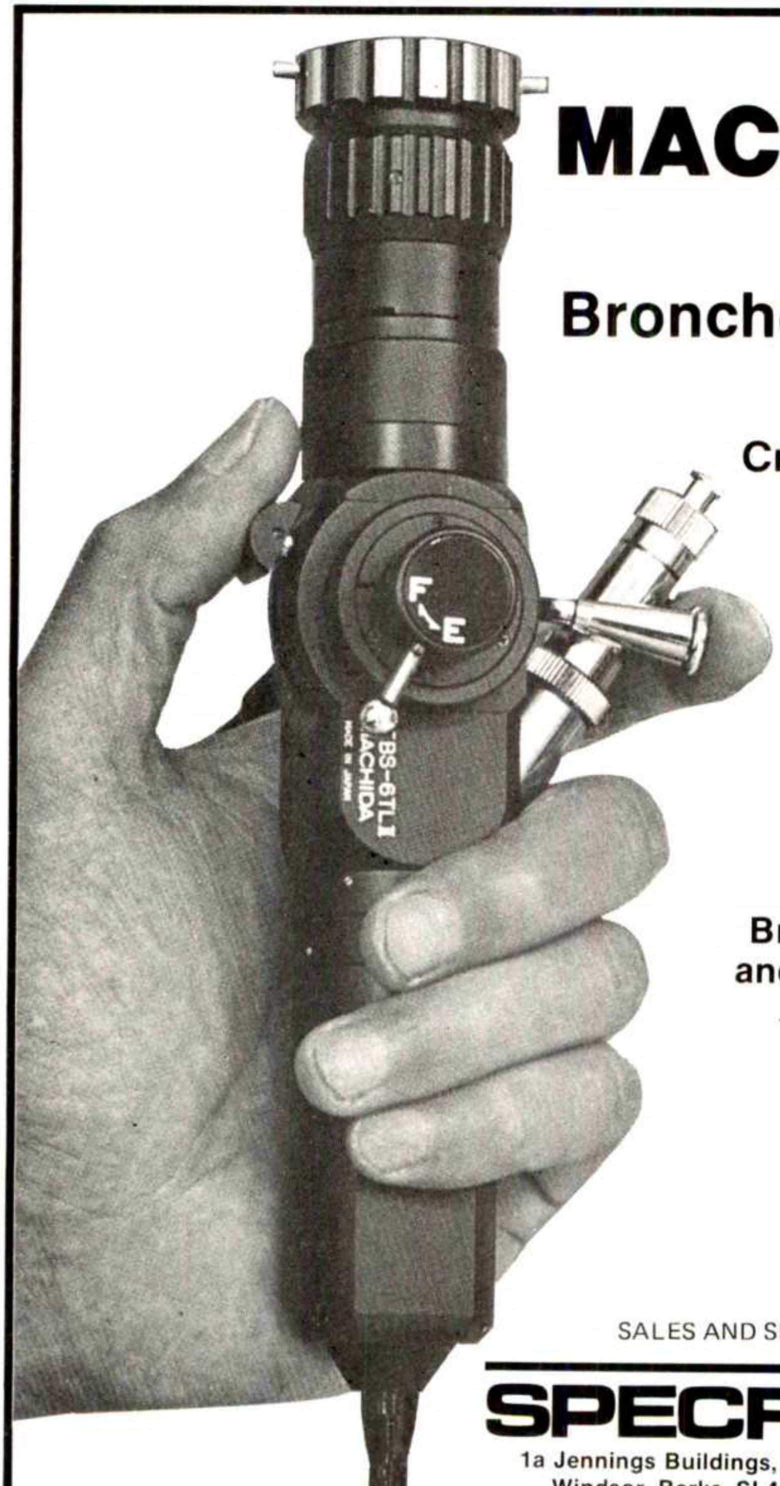

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THE TREATMENT OF SARCOIDOSIS BY LEVAMISOLE

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Summary

Five patients with persistent or progressive pulmonary shadowing due to sarcoidosis were treated with 150 mg levamisole daily and one patient with 150 mg twice weekly. Only the latter patient completed a 12-week course without unwanted side-effects. One of the remaining five patients on full dose completed the course but all experienced symptoms (nausea, malaise, influenza-like syndrome or arthralgia and skin rash) severe enough to cause five to stop the drug. Haematology and biochemistry, however, remained normal, with the exception of transient rise in transaminases in one patient. Radiology, pulmonary function and numbers of circulating T-lymphocytes (E-rosettes) were unchanged, but three patients developed increased intensity of delayed hypersensitivity (DH) skin tests using PPD, *Candida* and *Trichophyton* antigens; two of these patients also developed increased in vitro lymphocyte stimulation by mitogen and PPD antigen and the other developed a 'serum sickness' syndrome with evidence of circulating immune complexes.

INTRODUCTION

Sarcoidosis is associated with disturbed immunological reactions. Skin reactions of the delayed hypersensitivity type, including the tuberculin test, are depressed (Citron 1957). Other manifestations of delayed hypersensitivity have been demonstrated to be depressed in sarcoidosis including reduction in the number of T-lymphocytes in peripheral blood (Hedfors et al. 1974) and depressed transformation of lymphocytes by phytohaemagglutinin (PHA) (Hirschhorn et al. 1964; Buckley et al. 1966).

Levamisole, a synthetic antihelminthic agent, has the property of restoring depressed cellular immune responses to normal, both in vitro (Hokama et al. 1974; Lichenfeld et al. 1974; Pabst & Crawford 1974) and in vivo (Hokama et al. 1974; Tripodi et al. 1973).

We studied patients with sarcoidosis before, during and after treatment with levamisole to detect changes in clinical state and delayed hypersensitivity in vivo and in vitro.

Materials and Methods

Patients

Patients with histologically confirmed or Kveim-test-positive sarcoidosis were admitted to the study with informed consent. All had pulmonary shadows which had persisted or progressed

Table I. Clinical and immunological results

Case	*Test*	*Weeks during trial*						*Duration of therapy and dose*	*Adverse effects*
		−12	−6	0	Treatment period	+12	+18		
1	*DH skin tests*								
	PPD 1/100	0	ND	0		0	0	150 mg twice weekly for 12 weeks	Nil
	Candida	+	ND	+		+	+		
	Trichophyton	0	ND	0		0	0		
	LT								
	PHA	6.5	3.6	4.7		5.0	3.3		
	PPD	1.8	1.0	1.3		1.1	1.3		
	ER	48	57	52		47	ND		
2	*DH skin tests*								
	PPD 1/100	+	ND	+		+++	++	150 mg daily for 12 weeks	Intense tiredness throughout resolving over the 4 weeks following completion of the course
	Candida	+	ND	+		+++	+		
	Trichophyton	0	ND	0		++	0		
	LT								
	PHA	21.5	20.0	17.4		37.6	49.5		
	PPD	4.1	3.2	3.5		6.1	14.3		
	ER	42	39	45		34	40		
3	*DH skin tests*				*+1 week*				
	PPD 1/100	++	ND	ND	+++	++	++	150 mg daily for 8 days	At 7 days developed fever, arthralgia, headache, maculoerythematous rash resolving spontaneously over 6 days
	Candida	+	ND	ND	++	+	+		
	Trichophyton	+	ND	ND	++	+	+		
	LT								
	PHA	34.0	51.0	45.5	18.2*	39.6	42.5		
	PPD	4.0	4.5	3.7	1.7†	4.6	3.7		
	ER	68	55	62	58	ND	ND		

4	*DH skin tests*							
	PPD 1/100	0	ND	0		0	0	150 mg daily for 10 weeks	Persistent 'influenza-like' symptoms
	Candida	0	ND	0		0	0		
	Trichophyton	+	ND	+		+	+		
	LT								
	PHA	14.0	5.4	8.9		21.2	12.4		
	PPD	2.1	1.1	1.9		0.8	2.3		
	ER	63	ND	69		42	58		
5	*DH skin tests*				*+3 weeks*				
	PPD 1/100	0	ND	0	+	0	0	150 mg daily for 3 weeks	Malaise, lassitude, nausea, anorexia and arthralgia occurred with transiently raised serum transaminases (SGOT 46 u/litre, SGPT 47 u/litre)
	Candida	0	ND	0	++	+	+		
	Trichophyton	0	ND	0	+	+	0		
	LT								
	PHA	2.0	8.2	ND	82.5	24.0	19.0		
	PPD	1.3	1.9	ND	7.6	4.2	1.8		
	ER	40	53	46	52	ND	41		
6	*DH skin tests*								
	PPD 1/100	0	ND	0		0	ND	150 mg daily very irregularly for 12 weeks	Severe nausea
	Candida	0	ND	0		0	ND		
	Trichophyton	0	ND	0		0	ND		
	LT								
	PHA	13.2	10.0	21.4		13.0	17.4		
	PPD	1.3	1.1	0.5		1.2	0.8		
	ER	36	45	45		52	39		

DH = delayed hypersensitivity; LT = lymphocyte transformation; ER = erythrocyte rosettes; PHA = phytohaemagglutinin; PPD = purified protein derivative; ND = not done.

* In normal serum = 41.5.

† In normal serum = 3.9.

for more than a year but had no radiographic evidence of major fibrosis. Patients were observed for 12 weeks prior to the start of levamisole which was prescribed in a dose of 150 mg for 12 weeks and followed by a six-week observation period.

Methods

Time of tests. Skin tests, chest radiograph and pulmonary function tests were carried out 12 weeks before treatment, at the start of treatment (except pulmonary function), after 12 weeks of treatment and six weeks after treatment. Haematology, biochemistry, lymphocyte transformation and E-rosettes were carried out every six weeks starting 12 weeks before and ending six weeks after treatment.

Skin tests. The following antigens were used: purified protein derivative (PPD), *Candida albicans* (strain A) and *Trichophyton* mixed species (group 1) in 0.1% solution. The diameter of induration was measured and expressed as 0, +(1–5 mm), ++(6–10 mm), +++ (>10 mm).

Lymphocyte transformation was carried out by modification of a previously published method (Cole & Molyneux 1975) using PHA mitogen and PPD antigen in a dose-response manner in triplicate cultures, and duplicating these in autologous and normal serum to detect serum inhibitory factors. Results were expressed as stimulation indices (cpm of mitogen or antigen stimulated culture/cpm of unstimulated culture). Normal range: PHA = >45; PPD = >2.5 if sensitized.

E-rosettes (*ER*) were obtained by the method of Kaplan and Clark (1974) using sheep red blood cells (SRBC) stored for no longer than one week at 4°C in Alsever's solution. The sulphydryl reagent 2-aminoethylisothiouronium bromide (AET) was obtained from Sigma Chemicals. AET-treated SRBCs were washed in phosphate buffered saline at 4°C. Rosette-forming cells were visualized by fluorescent microscopy as described by Ramasamy (1974). Normal range: 63–81% of cells form rosettes.

Haematology and biochemistry. Full blood count, serum electrolytes, calcium and proteins, blood urea and liver function tests were carried out.

Pulmonary function tests. Dynamic and static lung volumes and carbon monoxide transfer factor were measured.

RESULTS

Clinical and immunological results in six patients are shown in Table I. Five patients receiving 150 mg daily experienced unpleasant symptoms and only one highly motivated patient (Case 2) completed a full course of the drug. Case 1 took 150 mg daily on only two days a week and suffered no side-effects. No change in radiographs or pulmonary function tests was seen and no abnormality in haematology or biochemistry was seen with the exception of a transient rise in serum transaminases in Case 5.

Immunological results showed that Cases 2, 3 and 5 developed increased intensity of reaction of their delayed hypersensitivity skin tests whilst on treatment with levamisole. Two of these (Cases 2 and 5) were also shown to develop increased in vitro delayed hypersensitivity as measured by lymphocyte transformation to PHA and PPD; the third (Case 3) developed a significant titre of serum inhibitory factor to PHA lymphocyte stimulation during the period in which her delayed hypersensitivity skin tests increased in intensity and a 'serum-sickness' type of syndrome appeared. At the height of this drug reaction evidence of circulating immune complexes was found by an increase in C_1q binding; however, her C_3 level remained within normal limits and she did not develop evidence of renal dysfunction. The total number of circulating T-lymphocytes as judged by the rosette test did not change significantly in any patient but was below or at the lower limit of the normal range in all except Case 3.

DISCUSSION

The clinical results of this small study suggest that the use of levamisole in a dose of 150 mg daily for treatment of sarcoidosis produces intolerable side-effects. All five patients receiving this dose of the drug experienced unpleasant symptoms including anorexia, nausea, tiredness and an influenza-like syndrome. Only Case 2 completed a full course of the drug and this only because he was highly motivated. Case 1 took the drug in a lesser dose of 150 mg daily on two days a week and suffered no side-effects. No patient received any clinical benefit from the drug in the dose administered before the trial was discontinued.

It is interesting to note that two (Cases 2 and 3) of the three patients with an increase in delayed hypersensitivity skin test reaction intensity whilst taking the drug had positive skin test reactions prior to therapy, but it should be noted that the period of treatment of all but two patients was shortened by side-effects; had this not been the case increased in vivo or in vitro delayed hypersensitivity reactivity might have developed subsequently. However this did not occur in Case 1, who took the reduced dose of 150 mg levamisole on two days a week. We think that this is the first report of acquisition of both in vivo and in vitro delayed hypersensitivity in sarcoidosis during treatment with levamisole.

Previous use of levamisole in sarcoidosis has also been associated with side effects. In a study of 22 patients with sarcoidosis given the same dose of the drug for four weeks two patients deteriorated whilst one improved (Rosenthal et al. 1976). Urticarial rash was observed in three patients and no change in skin reactivity was found. In a study of cutaneous sarcoidosis (Veien 1977) 150 mg of the drug was given daily for nine days and thereafter 150 mg twice weekly for six months. The lesions of two patients were aggravated, requiring withdrawal of the drug, whilst two of 13 patients completing the course had clearing of their lesions. Use of levamisole in other diseases has also been associated with side-effects causing termination of trials, one example being a study of 69 patients with cancer in whom 22% developed gastrointestinal, 'influenza-like', skin and neurological disturbances (Parkinson et al. 1977).

It is concluded that levamisole in a dose of 150 mg daily cannot be recommended in sarcoidosis because of troublesome adverse effects in the absence of beneficial effect on the course of the disease.

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IN VIVO AND IN VITRO REACTIONS TO ANTIGENS OF *HAEMOPHILUS INFLUENZAE* IN BRONCHIAL OBSTRUCTION

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Summary

The frequency of precipitating antibody to heat-labile (H(1–2)) and heat-stable (HCW and HCF) antigens of *Haemophilus influenzae* was determined in patients with asthma, chronic bronchitis, cystic fibrosis and bronchiectasis and compared with that in a control group. This showed that the immune response of asthmatic patients to heat-stable antigens was different from that to the heat-labile antigens. Exposure to antigens of *H. influenzae* is common in all the disease groups.

Skin test reactions having the time course and macroscopic appearance of Type I (immediate) and Type III (late) were obtained after prick and intracutaneous skin testing with HCW antigen in varying concentrations in a group of patients with asthma, chronic bronchitis or cystic fibrosis and in a control group. It is suggested that IgE and short-term sensitizing IgG antibodies may be responsible for the immediate reactions while activation of the alternative pathway of complement by endotoxin contained in HCW could be responsible for the late reactions.

HCW antigens were shown to release histamine from non-sensitized human leucocytes; HCW and HCF antigens were shown to release histamine from non-sensitized human lung. None of the antigens tested had an effect on beta-receptors in tracheal preparations.

It is proposed that these reactions may contribute to the pathogenicity of *H. influenzae* in the lower respiratory tract.

Introduction

Early studies involving meticulous bacteriological examination of sputum (Mulder et al. 1952; May 1952, 1953) suggested that *Haemophilus influenzae* is a pathogen in chronic bronchitis. This conclusion appeared to be confirmed by the detection of precipitating antibody against *H. influenzae* in the serum of patients with chronic bronchitis (Burns & May 1967). Further studies suggested that *H. influenzae* is also an important pathogen in bronchiectasis and cystic fibrosis (Burns & May 1968).

The special characteristics of *H. influenzae* which make it an important pathogen in lower respiratory disease are not fully understood but it has been shown to have an inhibitory effect on mouse alveolar macrophages (Degre 1969) and on ciliary activity in tracheal organ cultures obtained from human fetus, chick embryo, rats and hamsters (Denny 1974).

Heat-labile antigens derived from the cytoplasm of *H. influenzae* are immunologically distinct from those that are heat-stable and derived from cell walls (Clarke 1977);

these antigens contain endotoxin (Branefors-Helander 1973; Van der Zwan et al. 1975; Van der Zwan 1977; Clarke 1977). This, in association with the production of antibody directed against the antigens, may be relevant to the organism's pathogenicity. A soluble toxin from *H. influenzae* Type B was originally described by Dubos in 1942.

The aims of the present study were (*a*) to determine the frequency of precipitating antibody to the heat-stable and heat-labile antigens of *H. influenzae* in patients with chronic bronchitis, bronchiectasis, cystic fibrosis and asthma; (*b*) to see if *H. influenzae* could participate in antigen–antibody reactions by skin testing with these antigens in the above groups; and (*c*) to see if *H. influenzae* could have a direct effect by testing the ability of antigens to release histamine from non-sensitized human leucocytes and human lung and assessing their effect on pharmacological receptors.

Materials and Methods

Detection of precipitating antibody

Standard immunodiffusion techniques as recommended by May (1972) were used. A positive precipitin reaction is determined by staining of the dried gel.

Antigens

H. influenzae specific cytoplasmic antigen (*H(1–2)*) was dissolved in phosphate buffered saline (PBS) pH 7.4 in a concentration of 1 g/litre and 10 g/litre. This antigen is so called because it is a purified form of antigen prepared by ultrasonic disruption of *H. influenzae.* It has been shown (Burns & May 1967) to separate out into five distinct positions designated H1 to H5 (H(1–5)) on immunoelectrophoresis at pH 8.2 against sera derived from a number of patients with chronic bronchitis. H1 is in relation to the cathode, H2 just to the cathode side of the origin and H3, H4 and H5 extending progressively from the origin to the anode. These studies further showed that antigen in positions H1 and H2 was specific for *H. influenzae*, while antigen in positions H3–H5 was shared by other Gram-negative organisms. Antigen used was prepared according to the method of Davis et al. (1974) with modification (Clarke 1977). The method was based on the fact that antigen with a positive charge, and therefore that shared by other Gram-negative organisms, could be removed if mixed with DEAE Sephadex-A25 at pH 8.0. In the modified technique complete removal is achieved by constant stirring of the Sephadex–antigen mixture for 24 hours at 4°C.

H. influenzae cell wall antigen (*HCW*) 10 g/litre in PBS was prepared by a hot phenol extraction method (Branefors-Helander 1973). The antigen is heat-stable and contains endotoxin (Clarke 1977).

H. influenzae culture filtrate antigen (*HCF*) 10 g/litre in PBS was prepared from a broth culture of *H. influenzae* and was shown to contain heat-stable and heat-labile components. The former contained endotoxin while the latter was felt to be cytoplasmic in origin and was destroyed by autoclaving for 10 minutes at 69 kPa (Clarke 1977). The heated antigen was used.

Selection of patients

Precipitating antibody study. Sera were obtained from groups of patients in the following categories:

1. *Controls.* Fifty-three patients without known respiratory disease and admitted to the Surgical ards of St Stephens Hospital, Chelsea. Smoking habits were not known.

W2. *Asthma.* Fifty-two patients attending Brompton Hospital and participating in a study of the relationship of infection to asthma. The diagnosis of asthma had been made by another physician before their entry to the study. Patients with features of chronic bronchitis were excluded although nine were smokers and 20 past smokers.

3. *Chronic bronchitis.* Sputum and serum from patients in this group had been sent to the department of bacteriology for investigation of respiratory infections. Fifty of the most recent sera in each group sent were selected for study. Diagnoses were confirmed by reviewing the patients' hospital notes on discharge which resulted in a reduction in numbers. No attempt was made to divide chronic bronchitis into simple and complicated but all had evidence of airway obstruction.

4. *Bronchiectasis.* Selection as for group 3.

5. *Cystic fibrosis.* Sera from patients with cystic fibrosis attending Brompton Hospital and Queen Elizabeth's Hospital, Hackney, were routinely sent to the department. Fifty of the most recent samples were selected.

Skin test study. Patients for this part of the study were selected as follows:

1. *Controls.* Eight healthy members of the laboratory staff.
2. *Asthma.* Patients within the group of 52 being followed as outlined above.
3. *Chronic bronchitis.* Four in-patients with this disease diagnosed by their attending consultant. Their blood was collected and tested separately from the 50 sera above.
4. *Cystic fibrosis.* Twelve in-patients at Brompton Hospital. Again their blood was collected and tested separately.

All the above patients were advised of the procedure and their consent obtained.

Reactions to antigens

Skin testing. Two methods were employed. (*a*) Prick skin testing with HCW antigen in a concentration of 1 g/litre and 10 g/litre in Coca's solution. (*b*) Intracutaneous testing with HCW antigen, 0.1 g/litre and 1.0 g/litre. Coca's solution was used as the control (Pepys 1975).The sterility of the antigens had been determined before use. Intracutaneous testing was carried out only in those patients who had a previously negative prick test to the same antigen. The skin test positivity of the patients and controls tested had been determined by previous testing with common allergens (Hendrick et al. 1975).

Results were defined as follows. A *positive immediate prick test reaction* was defined as a weal with a diameter of 1 mm or greater present at 15 minutes to the test antigens but not the control solution. A *positive late prick test reaction* was a swelling at the site of the test which was red, tender and itchy, present after six to eight hours and subsided by 36 hours. A *positive immediate intracutaneous test reaction* was a weal with a diameter greater than that elicited by the control with associated itch present at 15 minutes. A *positive late intracutaneous test reaction* was a swelling with the features mentioned above but with the same time course as for the late prick test reaction.

Ability to release histamine. Antigens (HCW, HCF and H(1–5)) were tested for their ability to release histamine directly from human leucocytes (Assem & McAllen 1970) and human lung (Assem & Schild 1968) into a control solution (Tyrode's solution). All test tissue had been thoroughly washed to remove any antibody which may have mediated release. The lung was obtained from a woman who had a lobectomy for carcinoma. Further clinical details and sera were not obtained. Upon removal, the lung was immediately transported in normal saline to University College, London, where the study was performed. Histamine concentration was measured biologically (Assem & Schild 1968).

Effect on pharmacological receptors. The effect on antigens on isolated intact guinea-pig trachea which had been prepared with isoprenaline to enable assessment of beta-receptor function was looked at according to the method of Coleman and Farmer (1971). If antigens were to have an antagonistic effect on beta receptors, more isoprenaline was required to cause 50% relaxation of the trachea (EC_{50}) in the presence of the sample than in its absence. This enabled a ratio to be calculated; if this was greater than 1, a blocking effect was present.

If the antigens had an agonist effect, the high resting tone in the preparations would not be regained after the addition of antigen. Antigens (HCW, HCF and H(1–5)) and a control were tested at a concentration of 0.03 g/litre. The control was dialysed freeze-dried culture media used to grow *H. influenzae* to obtain HCF (Clarke 1977).

Statistical analysis

The frequency of precipitating antibody against the antigens in sera from the disease groups was compared to the frequency in the control sera by χ^2 testing (Colton 1974).

RESULTS

Precipitating antibody

The frequency of precipitin reactions to the different antigens in the groups studied and the statistical significance of this frequency compared with the frequency in the control sera is summarized in Table I. The frequency of occurrence of precipitins to H(1–2) antigen was not significantly increased in asthmatic patients but it was for other the disease states. The same pattern applied for HCW antigen but not for HCF. In the case of HCF, the frequency of occurrence was significantly increased in asthma and chronic bronchitis. The frequency of precipitins to any of the antigens was then considered; again, asthma patients did not have a significantly increased frequency of precipitins. Finally, when the frequency of occurrence of antibody to the heat-stable antigens, HCW and HCF, was considered, all groups had a statistically significant increase. The last two studies show that patients could have precipitins to one, two or all three of the antigens studied.

Table I. Frequency of precipitating antibody to antigens of *H. influenzae* in asthma, bronchiectasis, chronic bronchitis and cystic fibrosis compared to a control group

Antigen	*Controls* ($n=53$)	*Asthma* ($n=52$)	*Bronchiectasis* ($n=39$)	*Chronic bronchitis* ($n=38$)	*Cystic fibrosis* ($n=50$)
H(1–2)	9	17*	19†	22‡	31§
HCW	6	13*	21§	21§	29‖
HCF	0	15‖	4*	8‡	1*
Combination of any or all of H(1–2), HCW, HCF	12	31*	29§	32§	39§
HCW and/or HCF	6	21†	23§	14†	30‖

* Not significant.
† $P<0.05$.
‡ $P<0.01$.
§ $P<0.005$.
‖ $P<0.001$.

Reactions to antigens in vivo

Prick skin tests. The results of prick skin testing to HCW antigen are summarized in Table II and divided up according to the patients' skin test positivity to routine antigens and HCW antigen concentration. It can be seen that immediate reactions could be produced but these were not related to skin test positivity to common antigens. Late reactions were more frequent but these were not related to a preceding immediate reaction, skin test positivity of the patient or to the presence of precipitating antibody to the antigen.

Table II. Prick skin testing results with *H. influenzae* cell wall antigen (HCW) in a control group and patients with asthma, chronic bronchitis and cystic fibrosis and relationship of late reactions to presence of precipitins

Skin test status	*Immediate reaction*		*Late reaction*		*Precipitins to HCW*	*Precipitins plus late reactions*
	1 g/litre	10 g/litre	1 g/litre	10 g/litre		
Controls						
Positive ($n=1$)	—	—	1	1	Not done	
Negative ($n=7$)	—	—	2	4		
Asthma						
Positive ($n=26$)	1	7	1	2	7	0
Negative ($n=17$)	1	2	1	3	5	2
Chronic bronchitis						
Negative ($n=4$)	—	—	4	4	1	1
Cystic fibrosis						
Positive ($n=6$)	—	1	3	3	4	2
Negative ($n=6$)	—	1	4	5	3	2

Intracutaneous tests. Results were as follows:

1. *HCW antigen at 1 g/litre.* Eight asthmatic patients (seven skin test positive and one skin test negative) who attended the out-patients on one day and who had previously had a negative prick test at this antigen concentration had an intracutaneous test performed. One skin test positive and one skin test negative patient produced a positive immediate reaction while all patients produced positive late reactions. The latter were determined at either six or 24 hours after the test; it was ascertained by telephone enquiry that all reactions had subsided at 48 hours. Only two of the eight patients had precipitins to this antigen.

2. *HCW antigen at 0.1 g/litre in patients on prednisone at the time of the test.* Ten patients on prednisone, seven asthmatic (one skin test positive) and three chronic bronchitis patients (all skin test negative) were tested. The minimum daily dose of prednisone being taken by a patient at the time of the test was 10 mg (mean 14 mg). The dose in one chronic bronchitic was not recorded. No immediate reactions were demonstrated but all patients had late reactions determined as described above. Only one of these patients had precipitating antibody to this antigen.

Reaction to antigens in vitro

Histamine release. HCW antigen was shown to cause significant release of histamine (12.4%) from non-sensitized human leucocytes at a concentration of 0.1 g/litre when compared to release obtained by control Tyrode's solution (5.8%). HCW antigen (0.01 g/litre and 0.1 g/litre) and HCF antigen (0.01 g/litre and 0.1 g/litre) caused significant release of histamine from non-sensitized human lung when compared to the control solution. In all cases release was greater than double the release achieved by the control (1%).

Beta-receptor function. The antigens H(1–5), HCW and HCF, when tested as described in a concentration of 0.03 g/litre, were shown to have no pharmacological agonist or antagonistic effect on beta receptors. HCW antigen did produce a ratio greater than one when beta-receptor antagonism was looked for; the concentration required to achieve this was far greater than would be expected if this was to be pharmacologically significant.

DISCUSSION

The frequency of precipitating antibody against *H. influenzae* antigen H(1–2) in the sera of the patients we studied, when compared to controls, confirms the earlier studies of Burns and May (1967, 1968). The frequency of precipitin reactions to HCW and HCF antigens has not previously been determined in patients with respiratory disease. Asthmatic patients appear to react differently to heat-stable cell wall antigens of *H. influenzae* in that a statistically significant number of asthmatics had precipitating antibody to HCF and to a combination of either HCW and/or HCF when compared with controls. This difference was not seen to antigens (H(1–2)) obtained from the cytoplasmic heat-labile antigens. It is of interest that the method of preparation of this antigen has been shown to remove much of the endotoxin activity which is associated with the heat-stable components (Van der Zwan 1977). As the specificity of these heat-stable antigens has not been determined some of the precipitin reactions to them may represent cross-reactions with other bacterial species (Clarke 1977).

By using a combination of antigens of *H. influenzae*, it has been demonstrated that a significant number of our patients have antibody to one or other of these antigens, suggesting exposure to them. Two of these antigens, HCW (Branefors-Helander 1973; Clarke 1977) and HCF (Clarke 1977), have been shown to contain endotoxin.

The increased frequency of reaction of asthmatic patients to the cell wall antigens without an increased frequency of reaction to cytoplasmic antigens may reflect an increased resistance to colonization and invasion by the organism. The frequency of reactions to any or all of the antigens in the other groups does not lend support to the idea that antibodies to the heat-stable antigens are protective (Bull & Smith 1977).

The observation that antibodies are produced to different antigens of *H. influenzae* in these disease groups and that several of these antigens contain endotoxin suggests several mechanisms of pathogenicity for this organism. Microbial pathogenicity in general is poorly understood (Smith 1972), and the pathogenicity of *H. influenzae* in respiratory disease is not universally accepted (Tager & Speizer 1975; Bell 1976). A hypersensitivity reaction on the part of the host to an organism or its products may, however, render it pathogenic (Coombs et al. 1975) and this does not appear to have been taken into account by those who doubt the pathogenicity of *H. influenzae*. This reaction is the mechanism for one of the respiratory syndromes elicited by *Aspergillus fumigatus* (Pepys 1969).

To explore the possibility that immunological reactions were occurring to antigens of *H. influenzae* in patients with various respiratory disease skin testing with HCW antigen was carried out. Results with prick testing and intracutaneous testing indicated that reactions having the macroscopic appearance and time course of Type I (immediate) and Type III (late or Arthus) reactions could be produced.

Type I reactions occurred in skin test positive and negative subjects; the antibody mediating the reaction in the former group, if one was responsible, was likely to be specific IgE (Stenius et al. 1971). These reactions also occurred in skin test negative subjects, the antibody in some may be specific IgE but in this group short-term sensitizing (STS) IgG could be responsible. A study by Longbottom et al. (1976), which shows that STS IgG antibody mediates Type I reactions to the polysaccharide or heat-stable antigens of *Candida albicans*, supports this.

The late reactions, although not biopsied, had the macroscopic features of a Type III reaction. Some features of these reactions have caused problems of interpretation of skin tests using bacterial antigens in previous studies (Hajos 1960; Hampton et al. 1963; Pepys 1975). Such features were the lack of relationship to a preceding Type I reaction, the presence in control subjects, the lack of relationship to detectable precipitating antibody with the methods used and the failure of prednisone in the doses used to inhibit the reaction. Rather than dismiss these reactions as being toxic or non-specific, it may be possible to explain them knowing that this antigen contains endotoxin which non-specifically activates the alternative pathway of complement (Goltze & Muller-Eberhard 1971). This would postulate a Type III like reaction being produced without the necessity for antibody. The clinical significance of these reactions in any individual is then determined by a knowledge of those conditions in which *H. influenzae* is regarded as clinically significant (May 1975). This suggested mechanism may explain results of studies by Hajos (1960) and Van der Zwan et al. (1975) in which patients and controls challenged with the whole organism developed bronchoconstriction.

Apart from hypersensitivity reactions to these antigens, direct effects of these antigens on the host were considered. The first effect considered was the ability of these antigens to release histamine from human leucocytes and human lung, studied in a way that excludes the possibility that any release is mediated by antibody. This study has shown that HCW caused release of histamine from human leucocytes while both HCW and HCF caused release from human lung. This release, if found to take place in vivo, could contribute to the clinical and pathological features of these disease states. Support for in vivo release of histamine in chronic bronchitis and extrinsic asthma has come from a study by Turnbull et al. (1977) in which histamine was demonstrated in the sputum of all patients with these diseases.

The effect of the antigens on beta-receptors in isolated guinea-pig tracheal preparations was also studied. HCW antigen was inhibitory, but the concentration used to achieve this was so great that it cannot be clinically significant.

This study suggests that *H. influenzae* is involved in asthma, chronic bronchitis, bronchiectasis and cystic fibrosis. Several mechanisms are proposed to explain its pathogenicity. It would appear that lower respiratory tract involvement by *H. influenzae* can contribute to the pathogenesis of these conditions. The extent of this contribution may be determined or modified by factors as genetic make-up and atopic status of patients, their smoking habits, pre-existent damage to their bronchi and impairment of local defence mechanisms.

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ANGIOTENSIN-CONVERTING ENZYME IN SARCOIDOSIS: A BRITISH STUDY

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Summary

Serum angiotensin-converting enzyme (ACE) activity was measured in 18 healthy controls, 26 patients with active sarcoidosis, 13 patients with inactive sarcoidosis and seven patients with extensive tuberculosis. The serum ACE activity showed no significant difference between male and female in the control or sarcoidosis groups. There was no correlation between ACE activity and age except in the female active-sarcoid group. ACE activity in the active-sarcoid group was significantly higher than in the control, inactive-sarcoid and tuberculosis groups. The ACE activities at Stages I, II and III of the disease were not significantly different.

INTRODUCTION

The presence of angiotensin-converting enzyme (ACE) in horse plasma was first described by Skeggs et al. in 1956. Interest in ACE started a decade later when it was found that angiotensin I is converted to angiotensin II in the pulmonary circulation and that angiotensin II is not metabolized during passage through the lung (Ng & Vane 1967 1968; Biron & Huggins 1968; Bakhle et al. 1969). ACE is a halide requiring dipeptidase which catalyses the reaction:

$$\underset{\text{(Angiotensin I)}}{\text{asp} - \text{arg} - \text{val} - \text{try} - \text{ile} - \text{his} - \text{pro} - \text{phe} - \text{his} - \text{leu}} \longrightarrow$$

$$\underset{\text{(Angiotensin II)}}{\text{asp} - \text{arg} - \text{val} - \text{try} - \text{ile} - \text{his} - \text{pro} - \text{phe}} \quad + \text{his} - \text{leu}$$

During this reaction angiotensin I, a relatively inactive decapeptide in the renin system, is cleaved at its carboxyl end to the pressor octapeptide angiotensin II and L-histidyl–L-leucine. Enzyme activity can be detected directly in the blood but its concentration is 30 times greater in lung tissue (Cushman et al. 1971). It is thought to reside within the pinocytotic vesicles in the capillary endothelial cells of the lung and to act upon angiotensin I in the pulmonary circulation (Bakhle 1968; Smith & Ryan 1971; Ryan et al. 1972).

The first indication of the value of serum ACE determinations as a diagnostic aid came from Lieberman (1974*a*, *b*), who reported for the first time 15 out of 17 elevated values in active sarcoidosis. Further reports from the United States (Silverstein et al. 1975; Ashutosh & Keighley 1976) and from Japan (Ueda et al. 1976) confirmed this initial finding.

In conditions other than sarcoidosis consistently elevated serum ACE activity has so far been demonstrated only in Gaucher's disease (Lieberman 1976).

The present work was undertaken to verify the value of measuring this enzyme in a group of patients with sarcoidosis in the United Kingdom.

Materials and Methods

Assay of serum ACE

The method used was described by Lieberman (1975). The substrate hippuryl-L-histidyl-L-leucine was obtained from the Aldrich Chemical Company Inc.

The calculation for the method as first described was later corrected by the author for a three-fold dilution (Lieberman 1976). The unit of activity is defined as nanomoles of hippuric acid released per minute at 37°C under standard assay conditions. The serum was separated on arrival at the laboratory and stored at −20°C.

Blood samples

Blood samples were obtained from four groups as follows:

Controls. Blood samples were obtained from 18 doctors and nurses; eight males and ten females aged 19–59 years (mean 36.7 years). All were in good health and not receiving any medical treatment.

Active sarcoid patients. This group consisted of 14 males and 12 females diagnosed as having active sarcoidosis with characteristic clinical and radiographic findings together with a positive Kveim test or the presence of non-caseating granulomas on biopsy. Most of these patients had a negative Heaf test. The patients were identified as having Stage I, II and III sarcoidosis by the usual criteria. The ages ranged from 19 to 57 years. The mean age of males was 35.1 (S.D. 8.1) years and of females 41.7 (S.D. 12.1) years.

Inactive sarcoid patients. This group consisted of six males and seven females aged 23–67 years (mean 42 years). These patients had been diagnosed in the past as having active sarcoidosis using the criteria mentioned above but were clinically symptom-free and had a normal chest radiograph at the time the blood specimen was obtained. The time interval between the regression of radiographic changes, clinical symptoms and the collection of blood was variable.

Tuberculosis patients. These comprised five males and two females aged 22–59 years (mean 42.2 years) suffering from extensive tuberculosis.

Statistical methods

Sex and age differences in the results from the male and female subjects in all groups were tested for statistical significance using the F-test and Student's t-test after previously assessing their distribution by the W-test of Shapiro and Wilk (1965). All groups were considered to have gaussian distributions as their W values were greater than 0.912. If a significant F-test was obtained a modified Student's t-test was used (Bailey 1973).

RESULTS

Individual results are shown in Fig. 1 and the mean and standard deviations of combined male and female results in Table I.

Table I. Mean serum angiotensin converting enzyme (ACE) activities in controls and patient groups and comparisons with the control group

Group	*No.*	*ACE activity* (units/ml; mean ± S.D.)	*Significance*
Control group	18	17.4±4.6	
Active sarcoidosis	26	35.5±10.7	$P<0.001$
Inactive sarcoidosis	13	22.5±4.4	$0.002<P<0.01$
Tuberculosis patients	7	18.3±5.4	N.S.

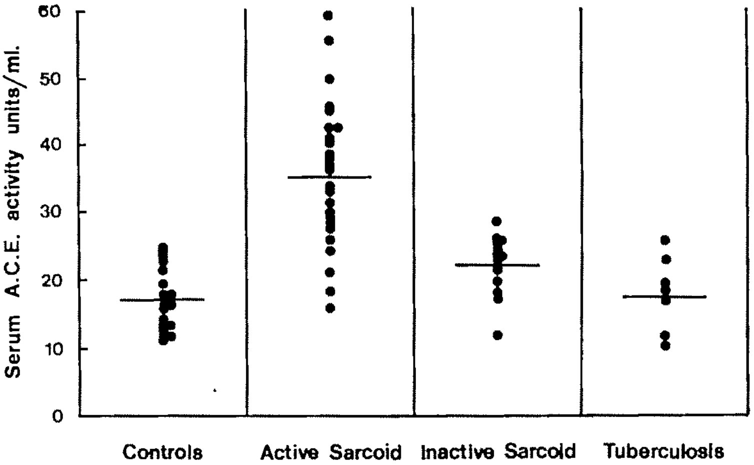

Fig. 1. Serum angiotensin-converting enzyme activity in patients and controls

Controls. The mean serum ACE in male and female control subjects was identical at 17.4 units/ml (S.D. in males 4.4 units/ml and in females 4.9 units/ml). There was no significant correlation with age in either sex.

Active sarcoid patients. The mean serum ACE in males was 35.0 units/ml (S.D. 12.7 units/ml) and in females 36.1 units/ml (S.D. 8.2 units/ml). These levels were not significantly different but there was a significant correlation ($P<0.05$) between female values and age. There was a highly significant difference between mean levels in patients with active sarcoidosis and in controls ($P<0.001$).

Inactive sarcoid patients. The group had a mean serum ACE activity of 22.5 units/ml. There was no significant difference between mean levels in males and females and no correlation with age. There was a significant difference ($P<0.001$) between the mean ACE results for the active and inactive sarcoid groups.

Stages of active sarcoidosis. The results from the Stage I, II and III sarcoidosis patients are shown in Table II. When tested for statistical significance no difference was obtained between the levels in Stages III and II or between those in Stages II and I.

Table II. Serum ACE activities found in patients with sarcoidosis at Stages I, II or III

Stage	*No.*	*ACE activity* (units/ml; mean ± S.D.)
Stage I	12	33.8 ± 11.8
Stage II	7	35.1 ± 12.9
Stage III	7	39.0 ± 6.6

Table III. Previously reported mean serum angiotensin-converting enzyme activities in sarcoidosis patients and controls

Reference	*ACE activity** (units/ml)		
	Control	Active sarcoidosis	Inactive sarcoidosis
Ashutosh and Keighley (1976)	17.6 (21)	20.6 (9)	40.5 (12)
Fanburg et al. (1976)	28.2 (84)	—	52.7 (56)
Friedland and Silverstein (1976)	32.2 (58)	—	—
Lieberman (1976)	22.8 (172)	20.6 (17)	47.3 (64)
Silverstein et al. (1976)	28.6 (63)	—	48.3 (58)
Ueda et al. (1976)	15.0	—	38.0 (30)
Studdy et al. (1978)	34.0 (80)	—	59.0 (24)

* Figures in parentheses indicate the number of patients.

Tuberculosis patients. This very small group had a mean serum ACE activity of 18.3 units/ml.

DISCUSSION

The results from this study confirm previous reports (Table III) that serum ACE is raised in patients with active sarcoidosis as compared with a control group. The mean value for the active sarcoidosis group was 35.5 units per ml, the inactive sarcoidosis group 22.5 units per ml and levels in both groups were statistically significantly higher than those of normal controls, which had a mean value of 17.4 units/ml.

That the inactive sarcoidosis group of patients was significantly higher than the control group is at variance with the reports of Ashutosh and Keighley (1976) and Lieberman (1976) who both reported no difference from their control groups. In all these studies the numbers tested were small and the differences may relate to sampling error due to small sample groups being used. Another possibility is that it might be related to the interval between regression of radiographic changes and clinical symptoms and the time when the blood was taken. This time interval was very short in some cases, raising the possibility of incomplete regression of sarcoidosis. However, all the ACE levels in inactive sarcoidosis were within the control range with one exception.

The difference in reported mean control values is quite marked (Table III); they range from 15 to 34.0 units/ml. This is despite similar methods being used with the exception of the values of 32.2 and 34.0 units/ml which relate to a fluorimetric assay. Apart from the value of 32.2 units/ml, for which no corresponding figure is given for active sarcoidosis, the reports with lower control values give lower values also for active sarcoid groups. The difference between the mean values in active sarcoid and in controls varies only from 19.7 to 25.0 units/ml.

Lieberman (1975) reported that serum ACE activity was greater in male than female control subjects of comparable age in a sample of approximately 200 subjects. Our control group consisted of only 18 persons and as the results did not show the same effect; it is tempting to attribute the discrepancy to a sampling error, but Fanburg et al. (1976) failed to show a significant difference between the sexes in a control group of 84 subjects.

Similarly there is little agreement on the effect of age on the serum ACE activity. Lieberman (1975) and Studdy et al. (1978) reported greater activity in subjects under 20 and 15 years of age respectively, but Ashutosh and Keighley (1976) reported that serum ACE activity increased with age. With similar numbers to the latter report we found that the serum ACE activity in controls did not correlate with age. There was, however, an increase in ACE activity with age in the female patients with active sarcoid, which was not observed in the male subjects or the group as a whole.

Despite the small sample size, the mean ACE activity of tuberculosis patients was similar to that of the control group and no statistical difference between the two groups was demonstrated. This is in contrast to the reports of Lieberman (1976) in which reduced ACE activities compared to control values were found in patients suffering from a variety of lung diseases including tuberculosis, and of Studdy et al. (1978) who reported two slightly elevated results from a series of 22 tuberculous patients.

This raises the question as to the source of the elevated serum ACE in active sarcoidosis. Lieberman (1976) showed, in an isolated experiment, that the ACE activity in a lymph node from a patient with sarcoidosis contained approximately 25 times greater activity than that obtained from a control lymph node at autopsy. Another report (Silverstein et al. 1976) described a 12-fold elevation in 14 sarcoidosis lymph nodes and no elevation from one tuberculous lymph node. These workers went on to investigate the enzyme's characteristics and found them to be similar to normal ACE with one exception, namely that ACE from the sarcoid lymph node was more heat-labile than that from normal lung or lymph node. This suggests the possibility that an abnormal ACE may be present in sarcoidosis and that the sarcoid granulomas may be actively synthesizing ACE.

At present the diagnosis of sarcoidosis depends on consistent clinical findings, radiographic changes, evidence of epitheloid cell granuloma from biopsy or a positive Kveim test. To confirm the diagnosis one may have to rely on an invasive technique or wait six weeks for the Kveim test to produce a reaction and this might delay treatment. The results obtained from sarcoidosis patients demonstrate the possible usefulness of measuring ACE activity in suspected cases, where many differential diagnoses have to be considered. Studdy et al. (1978) reported no difference in ACE activities at different radiographic stages. We confirm this, since no statistical difference was obtained between the activities from Stages III and II and II and I sarcoidosis patients.

The possible value of measuring serum ACE activity in diagnosing active sarcoidosis is well illustrated by the fact that 21 patients (81%) of those studied had enzyme activities that were higher than the upper limit (mean + 2 S.D.) of the control group. In contrast, only one patient with inactive sarcoidosis had a serum ACE activity higher than the upper limit of the reference range, yet, as mentioned earlier, the mean value for the inactive sarcoidosis group as a whole was statistically significantly higher than the control group. Our experience with this test would support the suggestion of Fanburg et al. (1976) that a raised serum ACE should aid the diagnosis in a number of patients who show the clinical features of sarcoidosis. It has also been reported (Lieberman 1976) that resolution of sarcoidosis or control with steroids can be monitored by repeated serum ACE determinations. Further evidence is presented in a recent report, which showed that ACE activities from steroid-treated sarcoid patients were significantly lower than those from untreated patients and by serial results in an isolated case (Studdy et al. 1978).

The only other reports of consistently elevated serum ACE activities have been in cases of Gaucher's disease (Lieberman 1976) and they are usually well above the levels seen in patients with sarcoidosis. This lipid storage disease can be readily distinguished by demonstrating an elevated serum acid phosphatase and the finding of Gaucher cells in tissue specimens. Elevations of ACE activity have been reported in a small percentage of patients with a variety of diseases (Lieberman 1975) and also by Studdy et al. (1978) who obtained up to 25% false positive elevations in a variety of other granulomatous disorders.

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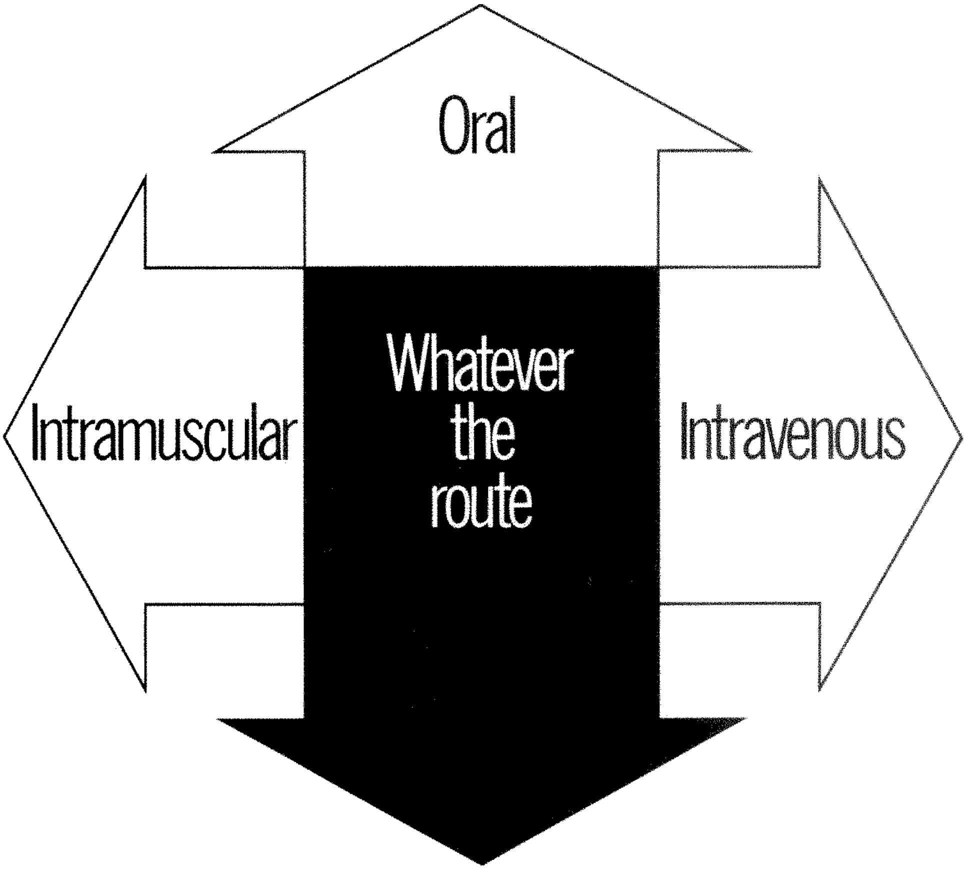

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Patients should be instructed in the proper use of the Rotahaler to ensure that the drug reaches the target areas within the lungs. They should also be made aware that Becotide Rotacaps have to be used regularly for optimum benefit.
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e of patients with chronic asthma

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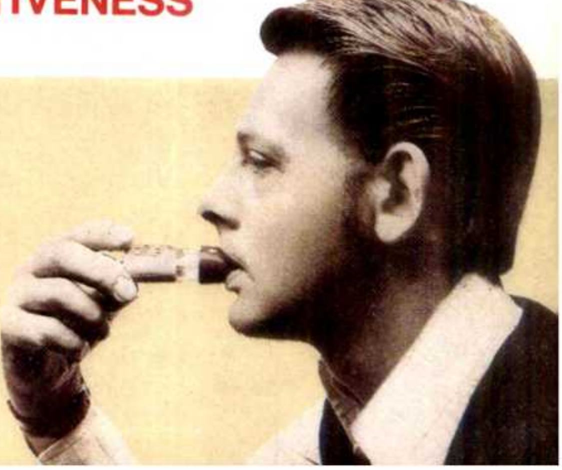

apparent ineffectiveness before the trial of a short course of systemic steroid in relatively high dosage has been given to control secretion of mucus and other inflammatory changes in the lungs.

When transferring patients to Becotide Rotacaps from systemic steroids, please refer to the detailed procedure described in the Data Sheet.

SIDE EFFECTS

No major side effects attributable to the use of recommended doses of Becotide Rotacaps have been reported. Candidiasis of the mouth and throat (thrush) occurs in some patients; patients with high blood levels of Candida precipitins, indicating a previous infection, are more likely to develop this complication. The condition usually responds to topical antifungal therapy without discontinuing treatment with Becotide Rotacaps.

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ROBERT KOCH (1843–1910): FOUNDER OF THE SCIENCE OF BACTERIOLOGY AND DISCOVERER OF THE TUBERCLE BACILLUS*

A Study of his Life and Work

ALEX SAKULA

Redhill General Hospital, Surrey

> There is properly no history: only biography
>
> RALPH WALDO EMERSON (1803–82)

Robert Koch was born on 11 December 1843 in Clausthal, a village in the Harz mountains, in the state of Hannover. His father, a mining engineer, was a local *Bergrat* (councillor) and Robert was one of a family of eleven, most of whom later went to America. Koch attended the local *Gymnasium* and then proceeded to Göttingen University, where he read mathematics and natural sciences. Having decided to take up medicine, he was a student under Professor Friedrich Gustav Jacob Henle (1809–85), famous for his pioneer studies in histology and author of *Miasma and Contagion* (1840), the latter possibly stimulating Koch's later interest in infection. Koch qualified M.D. in 1866, *cum extrema lauda*. He was then aged 23 (Fig. 1).

The next few years were spent in gathering a varied medical experience. He was briefly assistant in anatomy at Göttingen, then studied for a while under Rudolf Ludwig Karl Virchow (1821–1902), the pathologist and anthropologist. He then returned to Clausthal where he was in private practice for a short time, following which he obtained a hospital appointment in Hamburg.

In 1867, in Hamburg, he married Emily Fraatz, a friend of his childhood in Clausthal and daughter of the local *Intendant* (director). The marriage was at first a happy one and a daughter Gertrude was born to them in 1868. He returned to general practice in 1867, settling in Rakwitz, in the district of Bomst, a small town of four thousand inhabitants, but he also had to travel to see patients in the surrounding countryside.

The Franco-Prussian War (1870–71) was brewing and in 1870 Koch volunteered for the army, but was rejected because of his eyesight. However, in 1871, he again volunteered and was accepted for second-line duties in Lorraine and later served in a military hospital near Orleans. Koch was intensely nationalist in feeling, violently anti-French (he later showed a marked animosity to Pasteur) and greatly enthusiastic about the German victory.

On his discharge from the army in 1872 he obtained the Diploma of Public Health and took up the post of *Kreisphysicus* (district physician) in Wollstein, in Posen. He was

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* This account of the life and work of Robert Koch formed the basis of a Dissertation for the Diploma of History and Philosophy of Medicine and Pharmacy, Worshipful Society of Apothecaries. A contracted version of this paper was presented to the Osler Club of London in June 1978.

Fig. 1. Robert Koch in 1866

responsible for local public health, carried out vaccinations against smallpox and was required to report on epidemics. A keen naturalist, he devoted his spare time to study of local flora and fauna and searching for fossils. His wife presented him with a Hartnach microscope on his birthday and he set up a primitive laboratory and was able to turn his attention to the study of microbes in relation to infectious diseases.

In 1876, Koch investigated a disease prevalent in the sheep-raising districts, known as splenic fever or anthrax (German = *Milzbrand*; French = *le charbon*). A veterinary surgeon, Franz Aloys Antoin Pollender (1800–79), had discovered the organism *Bacillus anthracis* in 1849 and published his findings in 1855. Koch, however, was able to isolate the organism, study the life cycle from the spores and provide proof that it was the cause of the disease. He was very excited about his discovery and travelled to Breslau, where Professor Ferdinand Julius Cohn (1828–98) was investigating bacteria at the Botanical Institute, and was founder and editor of the journal *Beiträge zur Biologie der Pflanzen*. On 22 April 1876 and for the two following days Koch demonstrated his findings before Cohn and other eminent pathologists, including Julius Friedrich Cohnheim (1839–84) and Carl Weigert (1840–1904). Cohn was so impressed that he published this first account of the germ causation of disease in his *Beiträge* (29 May 1876). This paper remains one of the classics in the history of bacteriology. Koch was then invited to come to Breslau to engage in private practice as city physician, but also to continue his bacteriological researches.

The ensuing three years were exciting and fruitful. In 1877, Koch virtually laid the foundation of bacteriological technique by introducing the methods for examination of bacteria on cover slips and glass slides, the hanging drop technique, the fixing and staining of bacteria, their culture by the poured plate method, as well as the photography of the organisms. He also invented the method of steam sterilization. By 1878, Koch had demonstrated staphylococci and streptococci as the cause of wound infection. In 1880, he was proposed by Cohn as extraordinary member of the Kaiserliche Gesundheitsamt (Imperial Health Office) in the Louisestrasse in Berlin, where a small department was provided for Koch to continue his researches.

In 1881, Koch came to London and demonstrated his solid media and first pure cultures of bacteria at the First International Medical Congress. After the lecture, Louis Pasteur (1822–95) came forward and exclaimed: '*C'est un grand progres!*'. In the deliberations on tuberculosis he was so stimulated on hearing of the world-wide ravages of this disease that he returned to Berlin determined to find the causative organism. His work was rapidly successful and on 24 March 1882 he was able to make his famous report before an evening meeting of the Berlin Physiological Society. It is of interest that the tubercle bacillus was demonstrated in infected tissue and not in sputum on that occasion. Among those present were Virchow, known always to join in the discussion but on this occasion he remained silent with admiration. Also present was Paul Ehrlich (1854–1915) who later wrote: 'The evening stands in my memory as my greatest scientific experience.' Koch's paper, '*Die Aetiologie der Tuberkulose*' was published in 1882 in the *Berline Klinische Wochenschrift* and also contained the first statement of 'Koch's postulates':

1. The organism must be found in every case of the disease.
2. The organism must not be found as an accidental or harmless parasite in other diseases.
3. The organism, after its isolation from the body and cultivation in pure culture, must reproduce the same disease.

These postulates are rarely capable of being fulfilled; nevertheless, the importance of this severe discipline for the early workers in bacteriology cannot be denied. The news of the discovery of the tubercle bacillus spread rapidly around the world and Koch became an internationally famous figure: 'Koch's bacillus' and 'Koch's disease' became part of everyday medical jargon. Koch had a dry sense of humour and when asked how long it was necessary to flame a slide when staining for the tubercle bacillus, he replied, with a twinkle in his eye: 'As long as it takes to say "Robert Koch is a great man"!' While engaged in his bacteriological researches at the Imperial Health Office, Koch attracted around him a large number of exceptionally gifted pupils and collaborators. These included George Gaffky (1850–1918), a military doctor, who reported the culture of the typhoid bacillus in 1884, the organism having been previously demonstrated in 1880 by Carl Joseph Eberth (1836–1926). Another, also a military doctor, was Frederich August Johann Löffler (1852–1915) who discovered the glanders bacillus in 1882 and the diphtheria bacillus in 1884. In the years 1885–90, Koch also concerned himself with the application of the new bacteriological knowledge to public health, studying the organisms in water, soil and air and their relation to the prevention of disease.

The German Government encouraged him to turn his attention to other deadly infectious diseases. Cholera was rife in Africa and the East and in 1883 Koch was made head of the German Cholera Commission. He travelled to Egypt and India and again his investigations were successful in isolating the causative organism, the cholera vibrio, transmission of the disease being shown to occur chiefly via drinking water. On his return home he was awarded a national prize of 100 000 marks. Incidentally, while in Egypt, he discovered the bacillus responsible for Egyptian ophthalmia. The same organism was found in 1886 by John Elmer Weeks (1853–1944) to be the cause of 'pink eye'. The organism then came to be known as the Koch–Weeks bacillus.

In 1885, Koch was appointed Professor of Hygiene and Bacteriology at the Friedrich Wilhelm University in Berlin, but continued as advisor to the Imperial Health Office, where his research laboratories were housed in very cramped quarters. The German government therefore decided to provide him with a new research institute, commensurate with the growing importance of his work. In less than a year, the Koch Institute for Infectious Diseases was built on the Nordufen in the Wedding District of North Berlin. It was opened in 1891 with Koch as its first director, and was associated, for its clinical material, with the Charité Hospital until 1900, then with the Moabit Hospital (1900–1906) and thereafter with the Rudolf Virchow Hospital. The associated tuberculosis hospital was the Tuberkulose Kraukenhause at Heckeshoon on the Wannsee. The Koch Institute was badly damaged by bombing in the Second World War, but is now completely rebuilt.

Other brilliant research workers flocked to be taught by, and to work with, Koch and eminent abong these were Emil Adolf von Behring (1854–1917) who discovered diphtheria antitoxin, used the serum for the first time to save the life of a child on Christmas night 1890 and became the first recipient (1900) of the Nobel Prize for Medicine. Others at the Institute included Richard Friedrich Johannes Pfeiffer (1858–1945), who discovered the influenza bacillus in 1892; the American, William Henry Welch (1850–1934), the discoverer of the gas gangrene bacillus in 1892; Shibasabura Kitasato (1856–1931), who found the plague bacillus in 1894; as well as the great Paul Ehrlich (1854–1915) and August von Wasserman (1866–1925).

Following Koch's discovery of the tubercle bacillus in 1882, he continued his researches into tuberculosis, demonstrated in guinea-pigs the different reactions following secondary as opposed to primary tuberculous infection (the 'Koch phenomenon') and produced a glycerine extract of dead tubercle bacilli which he called tuberculin. He originally hoped that this 'old tuberculin' would prove to be an effective therapeutic weapon and when he announced it at the Tenth International Medical Congress in Berlin in 1890, the news spread around the world that Koch had discovered the miraculous cure for tuberculosis. However, old tuberculin proved to be a failure as a treatment and all hopes that had been raised were shattered—and, not least, those of Koch. When Koch introduced a more purified variety of tuberculin ('new tuberculin') in 1897, hopes were again raised that this might be a cure, but results were equally disappointing. However, the introduction of tuberculin proved to be a valuable diagnostic measure to distinguish those infected with the tubercle bacillus from the non-infected and later, in 1900, the introduction of BCG vaccine by Léon Charles Albert Calmette (1863–1933) and Jean-Marie Camille Guérin (1872–1961) gave tuberculin testing added importance as it separated those requiring from those not requiring vaccination. In 1901, Koch again visited London to attend the Third International Tuberculosis Congress and this was the occasion when controversy arose concerning the role of the bovine type of tubercle bacillus. Theobald Smith (1859–1934) had differentiated the bovine and human types of tubercle bacillus in 1898. At the 1901 Congress, Koch was thought to have said that the bovine type was harmless to man, but in fact he had merely maintained that the bovine type was less infectious and serious to man than the human type.

We may turn at this point from Koch's scientific activities and consider his personal and domestic life. In 1890, he bought his old parental home in Clausthal, where he was born, and had it renovated. His fellow citizens placed a tablet of honour on its walls. As Koch became more involved with his work and travels, his wife saw less and less of him and considered herself neglected. When he was at home, she behaved hysterically towards him and Koch resented this. In 1888, his daughter married a Dr Edward Pfuhl and left home. Koch was then more estranged from his wife and became depressed and paranoid, his colleagues noticing that he was suspicious and secretive towards them. He even considered going to the United States to join a brother who had emigrated there. In 1893, after 26 years of married life, his wife left him and they were divorced. Two months after the divorce, Koch married a young actress, Fraulein E. F. Hedwig Freiburg. She was aged 21, Koch was 50. The news of Koch's second marriage displeased government circles. The indignant burghers of Clausthal pulled down the tablet of honour from his house. Rumours about his social *gaffe* spread among the stiff-necked Berlin society and he became socially *persona non grata*. This may have been partly due to envy on the part of his medical colleagues, who considered that he had not risen to fame through orthodox academic channels at the university.

This social pettiness may have been the reason why, in his later years, Koch spent so much time travelling abroad, taking his young wife with him. From 1896, he was away on a long foreign trip every year. In that year he went, at the request of the British Government, to South Africa to study *rinderpest* (cattle fever) and while there he also investigated malaria, blackwater fever and tsetse sickness. In 1898–9, he was in Italy, Indonesia and New Guinea, studying childhood malaria and quinine prophylaxis. In 1903–5 he was in South Africa (Rhodesia) conducting research into horse-sickness and relapsing fever and he became increasingly interested in the protozoa in relation to human disease. In 1906–7, he was in East Africa (Tanganyika, then a German colony) on a sleeping-sickness expedition, conducting a trial of Atoxyl as a cure. In 1908, he was in the United States where he was feted, but on visiting the sanatorium at Saranac Lake with his young wife, Edward Livingstone Trudeau (1847–1915) is reputed to have remarked: 'You could not blame Koch, but what on earth could the young woman see in him?'! On the same trip he visited Japan, where he was greatly honoured. His old pupil and associate, Kitasato, now a Baron, had his own Institute of Bacteriology in Tokyo and when Koch visited him there a Shinto shrine was erected in his honour and, to this day, an annual tribute is paid there to Koch.

In 1904, Koch (then aged 61) retired from the Institute of Infectious Diseases, to be succeeded as director by Gaffky, who in his turn was followed by Löffler. Despite the social annoyances which he had to endure on his remarriage, Koch remained impervious to criticism and carried himself with great dignity. He continued to be universally honoured, was elected Member of the German Academy of Science, was elevated to the title of *Excellenz* and received the Nobel Prize for Medicine in 1905 for his work on tuberculosis.

His end came relatively quickly. He had enjoyed good health but in March 1910 he developed anginal symptoms and cardiac failure. On 21 May, he and his wife went to stay at the spa at Baden-Baden. On 27 May 1910, he was sitting dressed on the balcony of his hotel, facing a beautiful sunset, when his chin dropped and he died quietly. He was aged 67.

By his own wish his body was cremated and the ashes lie in a mausoleum which was erected in the south-west wing of his Institute. This is an impressive marble-lined room and above the casket containing his ashes there is a relief portrait of Koch by the Berlin artist, Professor Dr W. Schmarje. On the wall opposite to this is a marble slab on which is engraved a list of Koch's scientific achievements. Wreaths of flowers are placed there on the anniversary of his death. Adjacent to the mausoleum is a small museum containing historic memorabilia relating to Koch. There is a memorial plaque to Koch in the Central Pathological Laboratory, Dar Es Salaam, Tanzania (German East Africa in Koch's time), and also a memorial in Berlin, in Koch Platz, which is now situated in East Berlin.

As with all scientific advance, there was, over the centuries, a gradual build-up of an infrastructure of knowledge concerning the germ theory of disease but it was not until Koch's genius was brought to bear on the problem that real progress was made. His unravelling of the anthrax problem was on quite a different level from all the casual efforts and armchair philosophical speculation that had preceded him. His development of the laboratory methods (which are still in use today) demonstrated conclusively the causative relationship of micro-organisms and disease. Together with his French counterpart, Pasteur, he laid the foundations of the modern science of bacteriology.

Like all great men, Koch attracted around him a host of brilliant pupils of the calibre of Von Behring, Kitasato, Gaffky, Löffler, Welch and others, all of whom made important discoveries which have made them immortal. Any single discovery of Koch—the discovery of the tubercle bacillus being outstanding—would have ensured him a place in medical history, but when one considers his total achievement, he stands out as one of the medical giants of all time and medicine and humanity at large remain for ever indebted to him.

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A list of Koch's publications and of the contents of the Koch Memorial Collection in Berlin can be obtained from the author on request.

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CEFUROXIME IN SEVERE RESPIRATORY INFECTIONS: A DOUBLE-BLIND COMPARISON OF TWO DOSES

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Summary

Cefuroxime, a new cephalosporin, was given in doses of 750 mg and 1000 mg three times daily for 10 days to 99 patients in a double-blind comparison. Patients were moderately or severely ill with exacerbations of chronic bronchitis, often accompanied by pneumonia. Both doses were equally efficacious in improving the clinical state and sputum purulence and in maintaining the improvement.

INTRODUCTION

Cefuroxime is a newly developed cephalosporin with potential advantages over older cephalosporins including increased stability to beta-lactamase enzymes, high bactericidal activity in vitro against many organisms, especially *Haemophilus influenzae* (O'Callaghan et al. 1976; Eykyn et al. 1976) and lack of renal toxicity (Norrby et al. 1977). In an early study of cefuroxime (Pines et al. 1977*b*) 85% of 99 patients with severe purulent respiratory infections greatly improved and only six relapsed—an unusual success in our experience. Either 750 mg or 1000 mg three times daily were given according to medical preference. To determine the optimum dose for such infections we report here a subsequent comparison of these two doses in a double-blind study.

Patients and Methods

All patients admitted into the trial had purulent exacerbations of chronic bronchitis, pneumonia or infected bronchiectasis. Those with a definite history of cephalosporin hypersensitivity or anaphylaxis with penicillin were excluded, as were those with severe renal or hepatic dysfunction.

Patients were randomly allocated to receive unit doses of either 750 mg or 1000 mg cefuroxime sodium. The doses were given by intramuscular injection three times daily for ten days, the actual dose being unknown to the patient or the attending physician.

The clinical state of the patient was assessed daily together with an examination of sputum; bacteriological and biochemical tests were undertaken at the beginning and end of treatment; all investigations were the same as reported previously (Pines et al. 1977*b*).

RESULTS

One hundred and two patients were entered into the trial; three of these died within 24 hours of starting treatment and were therefore considered unassessable. Of the remaining 99 patients, 49 received 750 mg and 50 received 1000 mg of cefuroxime, each dose given three times daily.

The two dose groups were similar in patient composition. There were 12 women in each; 29 patients receiving 750 mg and 23 patients on 1000 mg had bronchial or lobar pneumonia, 15 and 20 respectively had extensive bronchiectasis and the remainder had acute purulent exacerbations of chronic bronchitis. More patients in the higher (34) than in the lower (26) dose group were considered to be severely ill, the remainder were moderately ill on admission. Thirty-six patients had received antibiotic therapy in the previous week; 20 of these were in the higher dose group.

The overall clinical response is shown in Table I. The mean time before obvious improvement could be seen was 3.4 and 3.7 days for the low and high dose groups respectively. In over three-quarters of patients in each group the sputum became mucoid or had only a trace of pus remaining and this occurred in a mean of 3.4 and 4.2 days respectively. Analysis shows no statistically significant differences ($P \leq 0.05$) between the two dose groups.

Table I. Clinical response and sputum changes

	750 mg ($n=49$)	*1000 mg* ($n=50$)
Clinical response		
Greatly improved	33 (67%)	34 (68%)
Moderately improved	8 (16%)	14 (28%)
Failed	8 (16%)	2 (4%)
Sputum after treatment		
Mucoid or with trace of pus	37	42
Remained purulent	12	8

Whenever possible those patients who had responded satisfactorily to treatment were observed in hospital for two weeks after treatment; of these 81 only 14 relapsed. In the 750 mg group one of the 40 patients observed had relapsed within one week; by the end of two weeks a further two patients had relapsed. In contrast in the 1000 mg group, seven of the 41 patients followed for one week relapsed; in the second week a further four patients relapsed; again the difference between the groups is not statistically significant. Improvement in white cell counts, sedimentation rate and peak flow rate showed no obvious difference between the two groups.

Bacteriology

Isolation rates before and after treatment in both groups are described in Table II. The results for two probable pathogens, *Haemophilus influenzae* and *Streptococcus pneumoniae*, and for a more doubtful pathogen *Escherichia coli*, are included. There were no differences between the two groups.

Untoward effects

Of the patients 95 were asked about pain on injection; 73 had none, 13 had slight and nine moderate pain, the latter receiving lignocaine for this with complete relief. While

Table II. Number of patients with bacteriological isolates before and after treatment

	750 mg		1000 mg	
	Before	After	Before	After
H. influenzae	15	3	13	3
Str. pneumoniae	7	1	9	0
E. coli	17	6	16	6
Total	39	10	38	9

receiving cefuroxime, one patient had diarrhoea and two developed mild rashes, one of the latter giving a history of previous penicillin sensitivity. Mild disturbances of hepatic function tests were found in 11 patients but in only one did they seem attributable to cefuroxime, the remainder being explained by congestive cardiac changes. The one exception was a 29-year-old female patient with infected bronchiectasis in whom the serum aspartate transaminase rose from 22 to 60 units after treatment, although other liver function tests remained normal and the patient's infection improved.

Discussion

In this study treatment with the higher dose of cefuroxime (1000 mg three times a day) produced immediate improvement in a greater proportion of patients in comparison with the lower dose (750 mg three times a day). However, this difference was negated by the high relapse rate in the higher dose group during the first week after treatment, although why this should have happened is obscure. In all other respects there was nothing to choose between the two doses. Thus 750 mg three times daily should become the standard dose for cefuroxime in purulent respiratory infections. If this dose seems insufficient it can safely be increased, probably to 1.5 g three times a day since 1 g has not proved to be significantly superior.

We have confirmed our preliminary impression that cefuroxime is highly successful in the treatment of purulent respiratory infections, including pneumonia. The low relapse rate is outstanding since most of the patients were elderly, with advanced and severe illness, and it seems superior to that which we have found with other antibiotics (Pines et al. 1977*a*). However, direct comparison with other antibiotics is required and we are currently comparing cefuroxime with ampicillin.

Acknowledgements

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PAPILLOEDEMA AND OPTIC ATROPHY IN CHRONIC HYPERCAPNIA

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Summary

Two patients are described with hypercapnia of 10 and 13 years duration. Both patients had papilloedema at different stages of their illness and one patient developed optic atrophy. Whether such changes are due to local retinal vascular changes, general change in cerebral vasculature or the result of raised intracranial pressure is unknown. A combination of all seems likely. Computerized axial tomography brain scan on Case 2 was compatible with cerebral oedema and the development of optic atrophy (Case 1) suggests cerebral oedema and consequent raised intracranical pressure as the major factor in the development of papilloedema in hypercapnic patients. Skull radiographic changes have not previously been reported in hypercapnia. The duration of the papilloedema is critical in the development of atrophy.

Introduction

Papilloedema in patients said to have pulmonary emphysema was first described by Cameron in 1933, who cited an earlier paper reporting the venous tortuosity in emphysema (Mackenzie 1882). Papilloedema is now a recognized, though rare, finding in chronic respiratory failure (Simpson 1948; Kay and Westlake 1954; Austen et al. 1957). We report two patients who suffered respiratory failure for more than ten years. The first patient developed papilloedema and optic atrophy early in the course of illness. The second patient developed papilloedema only in the last six months of illness. Papilloedema and optic atrophy in chronic respiratory failure are reviewed.

Case Reports

Case 1

A 41-year-old sales representative was admitted in January 1964 with a 24-hour history of ankle swelling and confusion. In January of the previous year he had complained of acute bronchitis for the first time and he was in bed for two weeks. On his first hospital admission there was fever, cyanosis, confusion and pitting oedema to the knee. The pulse was 110/minute. There was sinus tachycardia; blood pressure was 140/90. The liver was three fingers palpable. The fundi were normal. The haemoglobin was 16.4 g/100 ml, white cell count 17 100/mm^3 with an 86% neutrophilia. The PCO$_2$ was 7.6 kPa (56 mmHg). The chest radiograph revealed cardiomegaly with an increase in cardiothoracic diameter. An electrocardiogram showed right axis deviation. A diagnosis of cor pulmonale was made and treatment started with digoxin, mersalyl and tetracycline. The patient was discharged on the sixteenth day after a weight loss of 9 kg. The patient stopped smoking, having previously smoked 20 cigarettes a day for 20 years.

He was re-admitted in March 1965 when antibiotics were given for a bronchopneumonia for

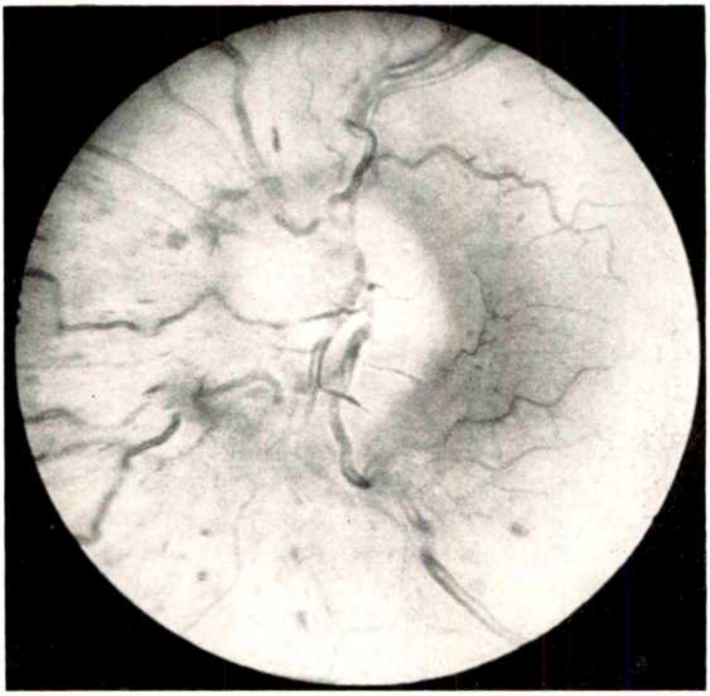

Fig. 1. Case 1. Optic disc November 1966 showing papilloedema

two weeks. In October 1966 further episode of heart failure occurred, the pH was 7.32 and the arterial $P\text{CO}_2$ 7.5 kPa (55 mmHg). The fundi were normal. He was discharged in November 1966 with improvement in respiratory function. Two weeks after discharge the patient noticed deteriorating vision both near and distant. Ophthalmic examination revealed gross bilateral papilloedema, tortuous veins, retinal haemorrhages and soft exudates. Vision in the right eye was 6/12 and in the left eye 6/24. A fundal photograph of the eyes at this time is shown in Fig. 1.

A skull radiograph was compatible with raised intracranial pressure; the sella was enlarged downwards with thinning of its dorsum and there was also thinning of the left anterior clinoid process. An EEG showed irregular low to medium voltage slow activity. The papilloedema persisted over the next 12 months, being more marked in the left eye. By October 1967 the vision in the left eye had deteriorated to seeing fingers at 1 m; the vision in the right eye was still 6/12. During 1968 progressive bilateral optic atrophy developed, though some oedema was still present in December 1968. In March 1969, on examination of the visual fields, the left eye could detect shadows only; there was a central scotoma in the right eye, with peripheral constriction of the visual field, and vision was 6/24. The optic discs were pale with reduced vasculature. There has been no deterioration in visual acuity or fundal appearance since this date. The patient was registered partially sighted. There were no further admissions for four years, but two subsequent admissions with cor pulmonale occurred in March 1973 and April 1976. He has been on continuous diuretics since 1964.

Respiratory function testing in February 1977 revealed an FEV_1 of 0.9 litres (pred. 3.4 litres), VC 2.6 litres (4.5 litres), FEV_1/VC 36%, TLC 9.6 litres (6.7 litres), FRC 8.1 litres (4.1 litres), RV 7.0 litres (2.3 litres), airways resistance 3.4 cmH_2O/litre/sec, TLco 10 ml CO/min/mmHg (29), mixed venous $P\text{CO}_2$ rebreathing method 8 kPa (60 mmHg).

At present the patient is well and though he has not worked for 14 years, he leads an active domestic life. A fundal photograph of the eye taken in 1977 is shown in Fig. 2.

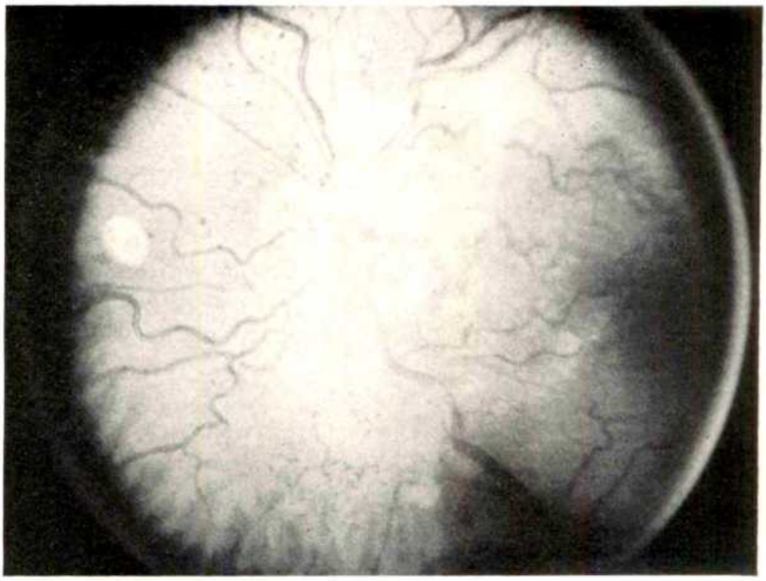

Fig. 2. Case 1. Optic disc March 1977 showing secondary optic atrophy

Case 2

A 49-year-old woman was admitted in June 1966 with a six-month history of cough, purulent sputum and headache. On examination there was cyanosis and mild confusion. Arterial blood gases showed a P_{O_2} 3.2 kPa (26 mmHg), P_{CO_2} 12.0 kPa (88 mmHg) and a pH 7.25. There was progressive deterioration in consciousness and the patient was ventilated through a tracheostomy for nine days. One month after recovery pulmonary function tests were performed; FEV 0.9 litres (pred. 2.2), VC 2.1 litres (2.8), FRC 3.2 litres (2.5), RV 2.4 litres (1.8) and TLC 4.5 litres (4.7). She was re-admitted in June 1968 after nine weeks of increasing cough and breathlessness. There was cyanosis and drowsiness, but no oedema. The mixed venous carbon dioxide by the rebreathing method was 8.5 kPa (62 mmHg) and on eight occasions over the next two weeks was never less than 7.5 kPa (55 mmHg). The patient was discharged home after three weeks.

She was admitted again in November 1970 with an exacerbation of bronchitis. Again there was no oedema. The mixed venous P_{CO_2} was raised between 8 and 10 kPa (55 and 70 mmHg).

The penultimate admission was in October 1976. The patient had a three-week history of severe headache. Ankle swelling had been present for one week. Examination revealed cyanosis, ankle oedema and bilateral papilloedema. On retinoscopy there was venous engorgement, loss of nasal margin, filling of the optic cup, and the disc was raised 3 D bilaterally. There were no haemorrhages or exudates. The pH was 7.32, P_{CO_2} 12.7 kPa (95 mmHg), P_{O_2} 5.7 kPa (40 mmHg) and the haemoglobin 19.6. The patient was discharged after three weeks of medical treatment.

Using computerized axial tomography a brain scan was performed in February 1977. This showed no evidence of a space-occupying lesion and the ventricles were considered small for the patient's age, suggesting brain oedema. The patient declined fundal photography. A skull radiograph showed definite loss of the lamina dura of the dorsum sellae in keeping with raised intracranial pressure. The rest of the pituitary fossa was normal. The final admission occurred later in February 1977 and the patient's condition gradually deteriorated until death March 1977. Permission for post mortem was refused. The patient smoked until a few days before her death. She received no diuretics till six months before her death.

DISCUSSION

The prevalence of papilloedema in respiratory failure was 10% in 108 cases (Simpson 1954) and 13% in another series of 70 patients (Flint 1954). Optic atrophy has been documented only once before (Freedman 1963), though failing visual acuity had been noted earlier without a description of the disc (Cameron 1933). How papilloedema occurs in chronic respiratory failure is not well understood. Factors operating could include raised venous pressure, polycythaemia, hypoxaemia and hypercapnia. Raised venous pressure alone, as in superior vena cava obstruction, does not cause papilloedema, though raised intracranial pressure occurs (Hinshaw & Rutledge 1942). Papilloedema can occur in the absence of cardiac failure and raised venous pressure in patients with chronic respiratory failure (Manfredi et al. 1961). Meadows (1947) considered that polycythaemia was, in part, responsible for papilloedema and this is supported by the finding of papilloedema in primary polycythaemia (Silverstein et al. 1962). The mechanism here may be due to local changes in the retinal circulation or dural sinus thrombosis. Austen et al. (1957), reviewing 11 cases of papilloedema in chronic respiratory failure from the literature, could find secondary polycythaemia in only four.

Papilloedema was observed in 12 out of 83 patients with cyanotic congenital heart disease (Petersen & Rosenthal 1972) and 57 of these patients showed retinal changes, which were related to an arterial oxygen saturation of less than 86% and a haemocrit of more than 49%; the retinal changes were most severe in those with the highest PCV. Reducing the haematocrit alone failed to produce retinal improvement in a small number of these patients and hypoxaemia was felt to be the main contributing factor. Hypoxaemia alone produces an increase in cerebral blood flow, though to a lesser extent than hypercapnia (Lennox & Gibbs 1932; Patterson et al. 1952).

In normal individuals breathing 6% carbon dioxide, cerebral blood flow increases by up to 20% (Fieschi & Des Rosiers 1976). Cerebral blood flow may to some extent determine cerebrospinal fluid pressure (Ryder 1952) and this increase in CSF pressure in chronic respiratory disease has been directly attributed to increased cerebral blood flow (Patterson et al. 1952). Westlake (1953) found in normal subjects that inhalation of pure oxygen did not elevate the CSF pressure while in patients with what he labelled emphysema an immediate rise in pressure occurred. In these patients during pure oxygen inhalation the $P\text{CO}_2$ as well as $P\text{O}_2$ rose. Westlake (1953) attributed the rise in CSF pressure directly to this carbon dioxide retention occurring as a consequence of hypoventilation. It would seem that a combination of hypoxaemia and hypercapnia is responsible for the development of papilloedema and that elevated venous pressure and polycythaemia may be considered minor contributory factors.

Studies on a patient with hypercapnia and papilloedema showed arterial pH lower and arterial $P\text{CO}_2$ higher than levels in the CSF (Manfredi et al. 1961). This inversion of the normal situation regressed as the patient's respiratory function improved. It was presumed that the brain tissue absorbed large quantities of carbon dioxide, establishing a brain–CSF–blood gradient, and that the high cerebral CO_2 produced cerebral vasodilatation, increased blood flow and vascular permeability and brain oedema. All these have been demonstrated experimentally (Culter et al. 1966). At necropsy in patients dying of respiratory failure with papilloedema engorgement of surface veins and flattening of convolutions, cerebellar pressure cone (Simpson 1954) and brain stem distortion (Miller et al. 1960) have been described. Such swelling has been attributed to cardiac failure (Spalter & Bruce 1964) though this is not invariable; 'advanced cerebral oedema' was described at autopsy with hippocampal gyrus and pes pedunculi notching in the absence of heart failure (Miller et al. 1960). A case of papilloedema with chronic respiratory failure and the pickwickian syndrome showed small ventricles on ventriculography. Cardiac failure was absent, but at autopsy marked vascular congestion of the brain was noted (Meyer et al. 1961).

It is surprising that optic atrophy so very rarely follows papilloedema in chronic respiratory failure. Freedman (1963) described a 44-year-old man who had papilloedema for five years after an episode of acute respiratory failure; despite improving respiratory function, the papilloedema progressed for four years. The disc slowly became less congested and was described as being full of pale glial tissue. Cardiac failure presented terminally and necropsy showed congestion of the brain with moderate tonsillar coning. Papilloedema and sustained elevation of intracranial pressure will eventually lead to optic atrophy. The transition from severe papilloedema to optic atrophy may take six to nine months (Walsh & Hoyt 1969). Papilloedema may persist despite respiratory improvement (Leggatt 1958) and lasted for more than two years in our case (Case 1); the duration of papilloedema in Freedman's case is unique.

A prerequisite for the development of optic atrophy is arterial narrowing in order to render the disc ischaemic (Walsh & Hoyt 1969). If papilloedema in chronic respiratory failure was solely due to local changes in fundal vasculature, the arteries as well as veins would be dilated and ischaemic atrophy would not occur.

Evidence that cerebral oedema rather than local factors cause the fundal changes is provided by both our cases. The skull radiograph changes in both cases reflect sustained and prolonged intracranial pressure and have not been previously described in hypercapnia; the changes were more marked in Case 1. The computerized axial tomography brain scan in Case 2, showing small ventricles for age, is compatible with brain swelling, though the water content of the brain cannot be assessed accurately by this technique. Chronic hypercapnia is regarded as an ominous sign; in a study in Britain, Simpson (1968) noted a 60% mortality within three years of the first elevated CO_2 reading, the remainder dying over the next four years. One of our patients died ten years nine months after presenting illness, the other is alive 13 years after presentation.

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Penetrating Sites

Amoxil's ability to penetrate bronchial secretions whether purulent or mucoid, may explain why it has been shown to be more effective than cotrimoxazole or ampicillin in preventing relapse in bronchitis.[1] *Amoxil also achieves significantly higher levels than ampicillin in both the maxillary sinus mucosa*[2] *and middle ear fluid.*[3]

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Penicillin Safety

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Amoxil
amoxycillin

Proves Successful

Indications· Cystitis, urethritis, pyelonephritis Bacteriuria in pregnancy Gonorrhoea. Skin and soft tissue infections Acute and chronic bronchitis Upper respiratory tract infections Otitis Media Pneumonia **Presentations**· Amoxil capsules: 250mg and 500mg; PL 0038/0103/5. Amoxil syrup· 125mg and syrup forte 250mg per 5ml, PL 0038/0108/9 Amoxil paediatric suspension: 125mg per 1.25ml, PL 0038/0107 Amoxil 3g sachet: 3g per 50ml, PL 0038/0238 Amoxil vials for injection. 250mg, 500mg and 1g, PL 0038/0221/2/5 The amoxycillin content per dose unit is present as the trihydrate in Amoxil oral preparations and as the sodium salt in Amoxil Injections Average daily cost for adults (250mg capsules t d s) is 35p and for children (125mg syrup t d.s.) is 24p at time of printing **Dosage: Adult Dosage** Oral 250mg three times a day. In severe infections doses should be doubled In simple, acute urinary tract infection in adults two 3g doses amoxycillin (Twin Pack) with 10-12 hours between the doses Injectable· 500mg IM 8 hourly (or more frequently if necessary) in moderate infections. 1g IV 6 hourly in severe infections **Childrens Dosage** (up to 10 years of age) Oral 125mg three times a day. In severe infections doses should be doubled Injectable· 50-100mg/kg bodyweight per day, in divided doses **Contra-indications:** Amoxil is a penicillin and should not be given to penicillin hypersensitive patients **Side-effects.** Side-effects, as with other penicillins, are usually of a mild and transitory nature they may include diarrhoea, indigestion or occasionally rash, either urticarial or erythematous. The urticarial rash suggests penicillin hypersensitivity, and the erythematous type rash may arise if Amoxil is administered to patients with glandular fever. In either case treatment should be discontinued. Since Amoxil is a penicillin, problems of overdosage are unlikely to be encountered Further information on Amoxil (regd) amoxycillin is available from:
Bencard, Great West Road, Brentford, Middlesex. Tel: 01-560 5151.

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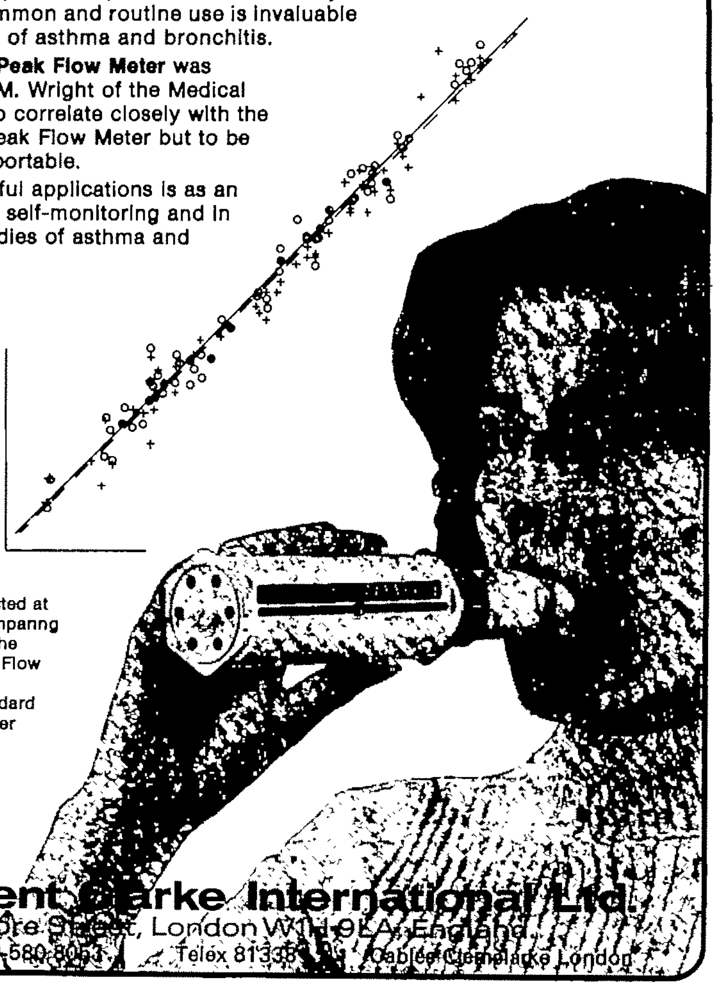

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HYDATID DISEASE PRESENTING AS TENSION PNEUMOTHORAX

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Summary

The case of a stockfarmer with hydatid disease which presented as a left tension pneumothorax is described. The diagnosis was not made until the patient underwent a thoracotomy for a complicating empyema.

Case Report

A 33-year-old Welsh stock farmer presented in December 1976 with a three-month history of cough with purulent sputum, a dull ache in the left side of his chest and slight effort dyspnoea. He had a severe bout of coughing and expectorated about 0.5 litre of straw-coloured 'cider like' fluid just before admission. He was mildly dyspnoeic but not cyanosed and had the signs of a left-sided pneumothorax. A chest radiograph confirmed a complete left pneumothorax with displacement of the mediastinum to the right and a small left-sided pleural effusion.

Other investigations showed a haemoglobin of 12.8 g/100 ml, white cell count of 7500/mm^3 without eosinophilia, and an ESR of 41 mm/hour (Wintrobe). Serum albumin was reduced at 33 g/litre and globulins increased at 40 g/litre, with raised beta- and gamma-globulin fractions. Urea, electrolytes, liver function tests and electrocardiogram were all normal. Mantoux test was negative at 1/1000 strength.

A diagnostic pleural aspiration was performed which revealed a straw-coloured exudate containing a few pus cells, but no growth on culture. No acid-fast bacilli were found on direct smear or culture and cytology was negative for malignant cells. Subsequently the pleural fluid became turbid with numerous pus cells and grew *Staphylococcus aureus* resistant to penicillin.

The patient was treated by insertion of an intrapleural tube connected to an under-water seal with suction applied via a Roberts pump for a total of eight weeks. The empyema was treated by repeated aspirations and flucloxacillin. The pneumothorax slowly resolved and the tube was withdrawn in February 1977. A residual empyema and some pleural thickening were seen on the chest radiograph. Further aspirations were unsuccessful and he was referred for thoracotomy, drainage and pleurectomy.

At operation the parietal pleura was found to be thickened and fibrous over almost the entire chest wall. The visceral pleural was not thickened. There was an abscess in the midst of the thickened parietal pleura which appeared to have a definite lining and communicated with a superficial abscess in the apicoposterior part of the left lower lobe.

Histology showed this to be a hydatid cyst. No scolices were present. Subsequently a hydatid component fixation test was found to be positive at 1/32 titre. A radiograph taken several months postoperatively showed no recurrence.

DISCUSSION

Hydatid disease is highly endemic in the Mediterranean countries, Middle East, South America and Australia but rare in Britain, although sporadic cases occur in Wales and

Sutherland. Pulmonary hydatid disease is usually symptomless, but when symptoms do occur these may be related to discharge of the cyst into the bronchial tree, causing cough and expectoration of watery fluid. If the cyst discharges into the cardiovascular system, urticaria or even anaphylactic shock may occur. Slight haemoptysis is frequent. Apparently it occurs as the cyst increases in size and destroys small bronchi and blood vessels by compression. Pneumothorax is a rare complication of pulmonary hydatid disease. Spontaneous pneumothorax has been described in areas where hydatid disease is endemic. Waddle (1950) described six such cases in 478 patients with pulmonary hydatid disease in Australasia. Tomalino (1959) described 16 cases of pneumothorax occurring in Spain while Bakir and Al-Omeri (1969) reported five cases of tension pneumothorax secondary to pulmonary hydatid disease in Iraq. In 88 Greek patients with pulmonary hydatid disease, three had hydropneumothorax (Xanthakis et al. 1972). In most of these patients the diagnosis of pulmonary hydatid disease was made from the chest radiograph. In the patient presented here the diagnosis was unsuspected.

In retrospect it seems likely that the expectoration of a large amount of watery 'cider-like' fluid which preceded his admission was due to the rupture of a cyst into the bronchial tree. Because of the persistence of an empyema and the development of pleural thickening he was referred for thoracotomy, drainage and pleurectomy.

This is the first case of pneumothorax complicating hydatid disease occurring in Britain that we have found in the literature. We would suggest that in patients who come from areas where sporadic cases of hydatid disease are known to occur, or indeed any patient presenting with a pneumothorax in an endemic area, should have the diagnosis of hydatid disease excluded. This is of some importance as surgery then becomes the treatment of choice.

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Short Communication

PERSISTENT ASTHMA AFTER TREATMENT WITH BETA-BLOCKING DRUGS

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Summary

Two atopic subjects with previously trivial asthma developed severe wheezing after receiving beta-adrenergic blocking agents. These drugs were discontinued but severe airways obstruction was still present more than 18 months later.

INTRODUCTION

In asthma beta-blocking drugs may result in a transient increase in the severity of airways obstruction. We report two patients in whom these drugs precipitated severe and prolonged wheezing. This has not previously been described.

Case Reports

Case 1

A 69-year-old woman was admitted in September 1976 with a two-month history of paroxysmal palpitations and effort angina. Since childhood she had had occasional bouts of mild asthma not requiring any treatment for 20 years. Blood pressure was 260/130 mmHg and there was no audible wheeze. A white cell count showed no eosinophils and an electrocardiograph during an attack of palpitations revealed paroxysmal atrial fibrillation.

She was treated with metoprolol 100 mg twice a day with good control of the angina, paroxysmal tachycardia and hypertension. Two weeks later the patient started to wheeze and in December 1976 was readmitted with severe wheezing and an unrecordable peak expiratory flow rate (PEFR). Metoprolol was discontinued and there was no response to inhaled terbutaline. Prednisolone 40 mg daily resulted in an improvement in PEFR but over the next 20 months it proved impossible to reduce the prednisolone dose below 15 mg daily and PEFR levels ranged from 95 to 420 litres/minute, depending on the prednisolone dosage. Intradermal prick tests gave positive reactions to the house dust mite.

Case 2

A 60-year-old man was admitted in July 1978. When aged 17 years he had wheezed whilst working in a biscuit factory; this was attributed to asthma resulting from hypersensitivity to flour and the wheeze did not recur when he changed his job two months later. In 1973 he attended an out-patient department with effort angina when an eosinophil count was normal. At this time he was treated with propranolol 160 mg daily.

Two months later (for no apparent reason) his general practitioner changed this to oxprenolol 240 mg daily until July 1977, when the dose was reduced to 120 mg daily because the angina had improved. In September 1977 he started to wheeze and oxprenolol was discontinued. In spite of this the wheezing increased and by May 1978 required treatment with prednisolone 40 mg daily. At admission in July 1978 he was receiving prednisolone 5 mg daily but was breathless at rest with a PEFR of 60 litres/minute and a normal chest radiograph. With intravenous hydrocortisone and oral prednisolone 40 mg daily the PEFR rose to 460 litres/minute. He was discharged on oral and inhaled corticosteroids. Prick tests gave positive reactions to house dust mite and feathers.

Discussion

It is well recognized that beta-blocking drugs may precipitate or worsen asthma and this phenomenon has recently been reviewed (Anderson & Jariwalla 1978). This deterioration has been regarded as temporary, resolving when the beta-blocking agent is discontinued. The unusual feature of these two cases was the persistence of severe asthma when the beta-blockers were stopped. In retrospect both patients had past histories of asthma of trivial severity and the more cardioselective agent metoprolol was used in Case 1 for this reason.

One of the authors (G.A.) has seen persistent severe asthma appearing for the first time after a single exposure to trichlorethane in one case and to fumes of burning oil in two others, all patients subsequently showing positive prick tests to the house dust mite. It seems probable that in atopic subjects a variety of transient chemical stimuli may trigger persistent asthma and conceivably the beta-adrenergic blocking agents may produce prolonged asthma in a similar way.

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Short Communication

RIFAMPICIN-QUINIDINE INTERACTION

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Many interactions have been described between rifampicin and other drugs. They include increased metabolism of warfarin, glucocorticoids and oral contraceptives, presumably by enzyme induction (Zilly et al. 1977). We report the first documented case of an interaction between rifampicin and quinidine.

Case Report

A 65-year-old man presented with progressive dyspnoea on exertion and recurring episodes of palpitations with lightheadedness. His only significant past medical history was of pulmonary tuberculosis treated in 1933 with repeated artificial pneumothorax and then between 1953 and 1955 with isoniazid.

Chest radiograph supported the diagnosis of a large tension hydrothorax on the right side. Although sputum, pleural exudate and pleural biopsy failed to show acid-fast bacilli on direct microscopy, there was a strong suspicion of tuberculous empyema. Therapy with rifampicin 600 mg daily and ethambutol 800 mg daily was initiated while awaiting culture reports.

His palpitations and dizziness were associated with bouts of frequent multifocal ventricular extrasystoles. Treatment with quinidine sulphate 300 mg every six hours suppressed his arrhythmia and each dose was subsequently reduced to 200 mg without loss of effect.

After one week of combined therapy, ventricular extrasystoles recurred with renewal of the symptoms. The dose of quinidine was increased to 300 mg and then 400 mg every six hours but no improvement was apparent clinically or on monitoring. Quinidine concentrations in plasma were greatly reduced (Fig. 1). Since rifampicin appeared to be the most likely cause of this reduction in plasma quinidine, it was replaced with isoniazid 300 mg daily.

The doses of quinidine and concurrent medications are shown in Fig. 1. Plasma quinidine concentrations in Fig. 1 were measured 1 to 1½ hours after the morning dose on the dates indicated. The quinidine concentrations returned to the previous value within one week of discontinuing rifampicin. The patient became symptom-free and monitoring indicated a resolution of the cardiac arrhythmia. The dose of quinidine was reduced when QT prolongation and mild nausea occurred.

Mycobacterium tuberculosis hominis was cultured from sputum and pleural fluid.

DISCUSSION

Possible causes of reduced quinidine concentration included poor availability due to poor compliance, change in pharmaceutical preparation, malabsorption or drug interaction in the gut. The same brand and batch of quinidine was used throughout; there was no change in bowel habit and the medications were given at different times making physical interaction unlikely. Compliance was confirmed by nurse observation. Since quinidine excretion in urine is pH-dependent (Gerhardt et al. 1969), urine was tested.

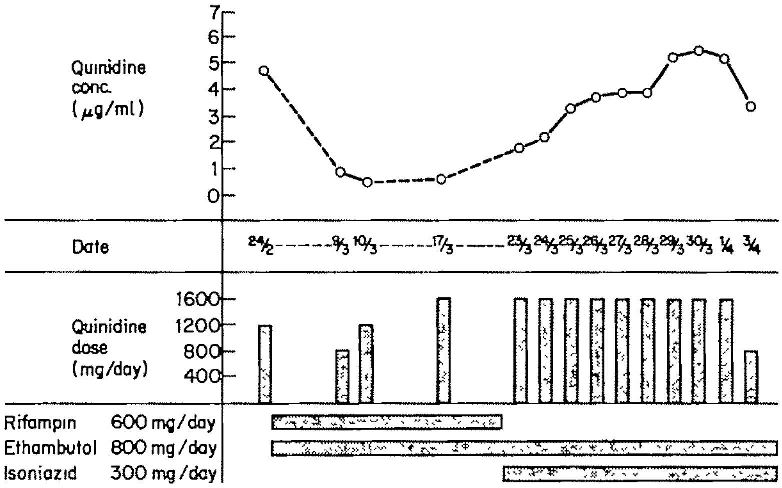

Fig. 1. Plasma concentrations of quinidine 1–1½ hours after morning doses. The dates, daily quinidine dosage and concurrent medications are indicated

daily but varied little between pH 5.5 and 6.5. Alteration of quinidine distribution should have resolved rapidly since rifampicin is almost totally eliminated within 24 hours. Enhanced elimination of quinidine appeared to be the only satisfactory explanation of our observations.

The topic of enzyme induction has been thoroughly reviewed by Remmer (1972) and Marshall (1978). The cytochrome P-450 enzyme system metabolizes a chemically and pharmacologically wide range of substrates, including endogenous and exogenous steroids, barbiturates, phenytoin, DDT and carbon tetrachloride. Increased quantities of enzyme and enzyme activity may result from prolonged exposure to certain substrates.

Although a number of techniques have been applied to assessing enzyme induction in man, only the reduction in drug half-life or steady state plasma concentration is specific for a given drug. There is considerable variation in the relationship between enhanced metabolism and other changes such as reduced antipyrine half-life, increase in plasma gammaglutamyl transpeptidase (γGTP), and increased urinary excretion of 6-β-hydroxycortisol or D-glucaric acid (Marshall 1978). Since rifampicin has recognized hepatotoxicity, γGTP concentrations were measured as part of liver studies but showed no change.

The metabolism of quinidine may be enhanced approximately two-fold by concurrent administration of phenobarbitone or phenytoin (Data et al. 1976). The effect of rifampicin on quinidine pharmacokinetics in our patient was even more dramatic, there being an associated drop in peak quinidine plasma concentrations from over 4 μg/ml to less than 0.5 μg/ml.

Rifampicin is increasingly used as a drug of first choice in the treatment of tuberculosis and the prophylaxis of meningococcal meningitis. Patients who receive other drugs should be carefully observed if those drugs undergo substantial oxidative metabolism, are therapeutically essential, and have a narrow therapeutic plasma concentration range.

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THE BRITISH THORACIC ASSOCIATION

The Annual Conference of the British Thoracic Association, jointly with the Swedish Thoracic Association, at Churchill College, Cambridge, on 2–5 July 1979. The following papers were presented.

BTA Study of Amoxycillin and Ampicillin in Bronchitis

A. D. Mackay

Southampton General Hospital

Amoxycillin is a semisynthetic penicillin with some potential advantages over ampicillin. Gastrointestinal absorption is better and unaffected by food and in chronic respiratory infections it gives high intrabronchial antibiotic levels when the sputum is no longer purulent. Amoxycillin has therefore been claimed to be more effective than ampicillin in the treatment of acute on chronic bronchitis.

The BTA study compared the efficacy and unwanted effects of amoxycillin with ampicillin in the treatment of exacerbations of chronic bronchitis. The two drugs have very similar half-lives in plasma after oral administration so both were given three times daily.

The study was a multi-centre, double-blind, between-patient comparison of ampicillin 250 mg or 500 mg or amoxycillin 250 mg or 500 mg, each given orally three times a day for seven days. All treatment was randomly allocated in balanced blocks of four.

199 patients were recruited from 31 centres. Those eligible were in-patients over 18 years of age, admitted with an exacerbation of chronic bronchitis (MRC criteria) and having purulent or mucopurulent sputum. Those who had already received five days or more of amoxycillin or ampicillin therapy, with carcinoma of the bronchus or lobar pneumonia or with allergy to penicillin or cephalosporins were not eligible.

Analysis of the results in terms of speed of conversion of sputum to mucoid and percentage of patients showing a satisfactory clinical response suggests that the theoretical advantages of amoxycillin are clinically unimportant in the treatment of a single acute exacerbation. Only in a small number of patients did diarrhoea lead to withdrawal of therapy on either drug. Drug rashes occurred in four patients only on ampicillin.

BTA Study of Short-course Chemotherapy in Pulmonary Tuberculosis

A. R. Somner and J. H. Angel

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After the first BTA study in 1972, it was possible to recommend that the duration of chemotherapy for tuberculosis in Britain be reduced to nine months. When the duration was reduced to six months, the relapse rate was 6% which was unacceptable. In the second BTA study of six-month regimens, pyrazinamide was added in the belief that it would reduce the relapse rate without increasing the toxicity. The first regimen consisted of isoniazid and rifampicin daily for six months supplemented initially by streptomycin and pyrazinamide for two months; the second, isoniazid and rifampicin daily for six months, was supplemented initially by ethambutol and pyrazinamide for two months; and the third, isoniazid and rifampicin for nine months, was supplemented initially by ethambutol for two months.

So far, 326 of 593 patients entered have completed the allocated chemotherapy and sputum conversion has occurred in 100%. The speed of the bactericidal effect of the regimens containing pyrazinamide was greater than that of the regimen which did not. A very few relapses have occurred so far but it is too early to say anything meaningful about them.

Hepatitis occurred in all three regimes. The incidence in the regimens containing pyrazinamide was 6% compared with 1.7% in the regimen which did not. In all patients who developed hepatitis, liver function returned to normal. However, measurements of liver function in all patients on four occasions during treatment showed no significant change in the mean values of bilirubin, alkaline phosphatase or aspartate aminotransferase.

It must be concluded that the addition of pyrazinamide to short-course regimens containing isoniazid and rifampicin appears to add to the frequency of hepatitis.

Hong Kong Chest Service/Tuberculosis Research Centre Madras/British Medical Research Council Study of three-month and two-month regimens for smear-negative pulmonary tuberculosis: results up to two years

D. J. Girling

Brompton Hospital, London

It is uncertain what proportion of patients with radiographically and clinically 'active' pulmonary tuberculosis, but whose sputum smears are repeatedly negative for acid-fast bacilli, require antituberculosis chemotherapy, or, for those who do need treatment, what duration is adequate. The duration of chemotherapy appropriate for patients with consistently smear-negative but culture-positive findings is also as yet unsettled.

In this study, 1212 Chinese patients, diagnosed at meetings of chest physicians from the Hong Kong Chest Service as having radiographically active pulmonary tuberculosis, but with sputum negative for acid-fast bacilli on five recent smear examinations, and who had not previously received antituberculosis chemotherapy, were randomly allocated to one of the four series:

1. SC (selective chemotherapy). Antituberculosis chemotherapy was not started until the activity of the tuberculosis had been confirmed bacteriologically on the initial or subsequent cultures, or by radiographic or clinical deterioration.
2. 2SHRZ. Streptomycin, isoniazid, rifampicin and pyrazinamide in standard dosages daily for two months.
3. 3SHRZ. The same as 2 above, for three months.
4. SPH/S_2H_2. A standard control regimen of streptomycin, PAS and isoniazid daily for three months followed by streptomycin and high-dosage isoniazid twice a week for nine months.

Of the 1212 patients, 1044 are currently assessable up to two years; 673 (64%) had negative sputum cultures on admission, 319 (31%) positive drug-sensitive cultures and 52 (5%) cultures resistant to isoniazid, streptomycin or both drugs.

Among the patients with negative cultures initially, 90 (51%) of 177 in the SC series had the activity of their disease confirmed during the two years, 67 (38%) by positive culture. In contrast, during the same period, only four (2%) of 169 2SHRZ patients, three (2%) of 164 3SHRZ patients and none of 163 patients on the control regimen relapsed bacteriologically.

Among the patients with drug-sensitive cultures initially, 10 (14%) of 72 2SHRZ patients, six (9%) of 70 3SHRZ patients, but none of 78 patients in the control series relapsed bacteriologically. Among the small number of patients with drug-resistant cultures initially, a few relapses occurred in all three treatment series.

It is concluded that the two short-course regimens were inadequate for patients with positive cultures initially. During a two-year period of follow-up, they largely prevented breakdown to active disease among patients with negative cultures initially, but their final assessment requires longer follow-up, which is continuing to five years.

The Changing Pattern of Laryngeal Tuberculosis

A. M. Hunter, J. W. Millar and
A. J. A. Wightman

City Hospital, Edinburgh

In 1924 Sir St Clair Thomson wrote 'there is no specific disease of the larynx as common as tuberculosis'. It was often a distressing terminal event in patients dying from pulmonary tuberculosis and was associated with advanced cavitated pulmonary tuberculosis. Scott Stevenson and Heaf in 1940 found it to be present in 15% of cases of pulmonary tuberculosis and St Clair Thomson found an incidence of 25% in 1948. It usually arose by direct airways spread of tubercle bacilli.

The pattern of laryngeal tuberculosis

has now changed and it frequently mimics laryngeal carcinoma. Patients present with hoarseness and painful dysphagia. Direct laryngoscopy may be avoided if an initial chest radiograph is taken.

We presented a series of ten patients diagnosed in Edinburgh over the past decade. They confirm the change in clinical pattern. There is a characteristic pattern in the chest radiograph suggesting haematogenous spread. A significant number have evidence of tuberculous disease in other organs. Sputum is not invariably positive for tubercle bacilli on direct smear.

A study has also been made of close contacts of the ten patients. No evidence of active disease was found and there was a low rate of positive tuberculin reactors. These findings suggest that the reputation of tuberculous laryngitis as being the most infectious type of tuberculosis is now unwarranted, though as sputum is often positive on direct smear it should be remembered that there is still a significant risk of infection.

Defective Yeast Opsonization in Tuberculosis

N. McI. Johnson, M. W. McNicol, A Kapoor, J. F. Mowbray and E. J. Burton Kee

Willesden Chest Clinic and St Mary's Hospital Medical School, London

The ability of sera to opsonize yeast particles was examined in sera from 80 patients who were known to be suffering with or have recovered from tuberculosis. Sera from 44 healthy controls were also studied. A modification of the assessment of serum opsonization of yeast phagocytosis by normal polymorphs was used, employing Coulter counting of the free, unphagocytosed particles.

Defective opsonization was found in 10 (12.5%) of the tuberculosis group but in only two (4.5%) controls ($P=0.1$, Fisher's exact test).

Table I shows the results when the tubercle patients were considered according to the regions affected by the disease. Patients with lung parenchymal disease showed a significant increase in the frequency with which the opsonizing defect was observed ($P<0.05$, Fisher's exact test).

The results and their significant were discussed.

Table I. Opsonizing defect in 80 patients with a history of tuberculosis

Group	*No.*	*Opsonizing defect*
Control	44	2 (4.5%)
Lung parenchyma	30	6 (20%)*
Hilar nodes	9	2 (22%)
Mediastinal nodes	13	1 (7.7%)
Extrathoracic nodes	29	1 (3.4%)
Other extrathoracic sites	14	2 (14%)
All TB patients	80	10 (12.5%)

* $P<0.05$ when compared with control (Fisher's exact test).

Current Effectiveness of BCG in Great Britain (1978)

V. H. Springett

Birmingham Chest Clinic

During 1978 in Great Britain there were 1638 notifications of tuberculosis in persons aged 15–24 years. In May 1979 survey forms had been received for 1214 (74%). There were forms for 621 immigrants after school age who were not available to take part in the schools BCG scheme, and 109 forms for persons who were not eligible for other reasons, mostly because they had either a positive tuberculin test or BCG vaccination earlier in childhood.

The remaining 484 patients had been eligible for the schools BCG scheme; 200 had been vaccinated; 105 had been found tuberculin-positive and 179 had not participated in the scheme. From these figures and the totals vaccinated or found positive in the schools scheme in the appropriate years, the notification rate for BCG vaccinated subjects is estimated as 5 per 100 000, and for tuberculin-positives 22 per 100 000 after allowing for under-reporting to the survey. Assuming the proportion of tuberculin-positives is the same in non-participants as in the rest of the population the notification rate in tuberculin-negative unvaccinated subjects is estimated as 12 per 100 000.

Comparison of the results for the 15–19 year age-group in England and Wales in 1978 with those from the similar study in 1973 shows little change in the rates for BCG vaccinated and tuberculin-positive subjects, but the rate for the tuberculin-negative unvaccinated group has fallen substantially. The protective effectiveness was 80% in 1973 and about 60% in 1978.

The apparent fall in protective effectiveness might be due to a decline in the potency of the vaccine used, but any change which resulted in a relatively high rate in BCG vaccinated subjects, or a relatively low rate in tuberculin-negative unvaccinated subjects aged 15–19 years in 1978, compared with the same age-group in 1973, could give the observed result.

BCG-induced Pleurisy in Guinea-pigs

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The pathogenetic mechanisms of pleurisy are still mainly unknown. Chemical and cytological data often give little guidance to diagnosis. One main reason for this is that in the clinical situation patients are investigated in a random phase on admission to hospital. Because of the difficulties of defining clinical pleurisy, we found it important to establish an experimental system. The guinea-pig, a classical animal of research and with a reasonable size, was used. Ten weeks or more after immunization by intracutaneous injection of 0.4 mg of BCG, 2 mg of BCG were injected into the right pleura. By this technique exudative pleurisy was produced on both sides in practically all animals. The appearance of the exudate was yellowish the first two days; from the third day onwards it was sanguineous. The effusion reached its maximum on days 7 to 11. On the seventeenth day there was generally a small effusion and on the twenty-first day the effusion had vanished. The pleural wall was mainly unaffected in the earlier stages, but from about the fourteenth day the pleural wall became swollen, rugged and there were adhesions. In the early stages granulocytes were the dominating cells of the effusions; from the third day onwards the exudate became predominantly lymphocytic.

The model was used for in vitro stimulation of DNA synthesis in lymphocytes. The effusion included a humoral high molecular fraction and did not stimulate lymphocytes *per se*, but enhanced stimulation by PHA and PPD. Lymphocytes from the pleura, which cannot be stimulated in the ordinary culture system, may possibly be stimulated in the presence of pleural fluid.

In conclusion, BCG-induced pleurisy in the guinea-pig gave reproducible experimental disease with well-defined stages and similarities to pleurisy in man.

Medical Research Council Survey of Notifications of Tuberculosis for England and Wales

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The present notification form used for tuberculosis provides information only on the age and sex of the patient and the site of the disease. Information about other aspects of the disease is important in planning policies for future tuberculosis control, particularly bacteriological status, radiographic extent of pulmonary disease and ethnic origin of the patient.

A survey to obtain this information was conducted in England and Wales for six months from 1 October 1978 to 31 March 1979 by the MRC Tuberculosis and Chest Diseases Unit. All chest physicians and general physicians with an interest in chest diseases gave their full cooperation in the survey. Consultants in other specialities, who notified patients with tuberculosis during the survey period, also cooperated. In addition, every Medical Officer for Environmental Health in England and Wales assisted in the survey.

Individual patient forms for a very high proportion of patients notified during the survey were received. A preliminary analysis of the findings for the first two months of this survey was presented, for which period reports by the clinician-in-charge have been received for over 99% of the patients.

Australian Experience with the Edinburgh Kveim Suspension

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The Edinburgh Kveim suspension has been tested in 53 patients at The St George Hospital. The Kveim suspension was prepared from the spleen of a patient with histologically confirmed sarcoidosis. The Kveim test was performed with 0.1 ml suspension given by intradermal injection; the injection site was biopsied four to six weeks later and examined histologically.

The Kveim test was reported as positive in 17 of 25 patients (68%) with sarcoidosis, including five of seven patients (71%) in whom the diagnosis was confirmed histologically by lymph node biopsy. In three patients with sarcoidosis the Kveim test was reported as equivocal. All patients with sarcoidosis had radiographic evidence of intrathoracic sarcoidosis, grade I: 16 patients (12 positive), grade II: four patients (two positive), grade III: five patients (three positive). The Kveim test was negative in 28 control patients, the majority of whom had diffuse fibrosing alveolitis, lymphoma or pneumonia.

There were no false positives. Foreign body reactions were sometimes a problem in histological interpretation. There were no side effects in patients given the Kveim suspension.

It was concluded that the Kveim test performed with the Edinburgh Kveim suspension is a useful and safe test for the diagnosis of sarcoidosis.

Prognostic Value of Doubling Time in Inoperable Lung Cancer

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The volume doubling time of 27 measurable primary inoperable pulmonary carcinomas was calculated. The prognostic value of the doubling time for survival was analysed in relation to age of the patient, initial size of tumour, histology, duration of symptoms and treatment. The survival was longest in slow-growing carcinomas. Small-cell carcinomas and other anaplastic carcinomas had the shortest doubling time. A close correlation was found between doubling time, survival and Feinstein's symptom staging.

Computerized Tomography in the Initial Staging of Oat (Small-cell) Carcinoma of the Bronchus

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Oat-cell carcinoma of the bronchus is a rapidly growing tumour which metastasizes early. The increased awareness of early metastases has lead to the use of chemotherapy in treatment either alone or combined with radiotherapy to the main tumour mass.

We have investigated 50 patients with this disease at the time of diagnosis using conventional staging techniques and computerized axial tomography of the thorax and abdomen in an attempt to define further the extent of intrathoracic disease and of metastases. Using the TNM classification of the American Cancer Association additional information available from the CAT scans increased the stage in 60% of cases. The definition of the intrathoracic tumour was improved with detection of *unsuspected* spread to pleura and mediastinum in 52% and hilar, carinal and paratracheal nodes in 40%. Unsuspected distant metastases to other organs were found in 28% and to para-aortic nodes in 8%.

Knowledge of true tumour extent is essential in the assessment of tumour response to treatment and in developing further treatment schedules. Definition of the tumour margins and hence measurement of its true extent was possible in a further 24% of cases following CAT scan.

The possible advantages of this more accurate staging technique has yet to be assessed. However, the increased ability of CAT scanning in defining primary tumour size and extent has important implications in improved radiotherapy planning to the mediastinum and primary tumour site in future trials.

Radiotherapy Alone or with Chemotherapy for Small-cell Carcinoma of Lung: Report of the MRC Lung Cancer Working Party

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Between March 1975 and April 1977, 253 patients were entered into the second MRC small-cell lung cancer study. These were randomized to receive treatment either by radiotherapy (RT) alone or radiotherapy followed by chemotherapy (RTC_3) (cyclophosphamide 500 mg/m^2, methotrexate 50 mg/m^2 intravenously every three weeks and CCNU 50 mg/m^2 orally every six weeks). Only limited disease patients were studied. After 17 exclusions, 236 are available for analysis (121 receiving RT, 115 RTC_3).

There was a significant improvement in survival in the RTC_3 group as compared with the RT only patients ($P = 0.002$). The median survival for the RT group was 25 weeks and for the RTC_3 43 weeks. The cumulative incidence of metastases was reduced in the RTC_3 group but cerebral involvement still remained a problem.

A brief description of the third MRC study currently in progress in which the influence of sequencing of the CT and RT is being studied was given. New proposals for a fourth MRC study were also presented. It is intended to investigate the influence of the addition of maintenance therapy to an intensive induction chemotherapy regime combined with locoregional radiotherapy.

Transbronchial Lung Biopsy in Sarcoidosis

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In disseminated lung diseases a new method was tried to obtain a histopathological diagnosis: transbronchial lung biopsy using fluoroscopy. The investigation was performed under local anaesthesia and the bronchofiberscope was inserted transnasally and via the trachea proceeded to the periphery of the lung. Under fluoroscopic guidance the site of biopsy could be precisely chosen 1–2 cm from the lung surface. It was important to collect specimens on the alveolar level to ensure satisfactory material from the lung and to avoid excessive bleeding.

Twenty-five patients with sarcoidosis in stage I (six), stage II (11) and stage III (eight) were diagnosed by biopsy from bronchial mucosa (11), cervical lymph node (three) and skin (one) and by Kveim test (five) and clinical course (five). Sarcoid diagnosis was confirmed in 10 cases and suspected in four. For comparison transbronchial lung biopsy was done in another 25 patients with disseminated lung diseases, but with a non-sarcoid diagnosis.

Table II. Results of diagnosis

Histopathological diagnosis	*Sarcoid*	*Non-sarcoid*
Epithelioid cell granulomas	10	—
Unspecified granulomas	1	—
Interstitial pneumonitis	1	1
Interstitial fibrosis	2	9
Pneumocystis carinii	—	1
Normal lung tissue	3	11
Insufficient material	8	3
Total	25	25

There was no bleeding exceeding 10 ml, but three patients had a pneumothorax, one of which was treated by suction drainage.

Transbronchial lung biopsy using bronchofiberscope under fluoroscopic guidance is a safe and easy procedure, which has a reasonable diagnostic yield in sarcoidosis and other disseminated lung diseases and a low incidence of complications.

Multiple Pleural Biopsies Using the Abrams' Pleural Biopsy Punch

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The standard method of using the Abrams' pleural biopsy punch is to take one or occasionally two biopsies during a pleural aspiration and to repeat the procedure at a different site if the initial biopsy is negative. The present report describes the results of taking multiple pleural biopsies, up to ten, from the same site during a single aspiration procedure in 55 consecutive patients with pleural effusions. Each of the 271 biopsies was sectioned at three levels, except for 11 in which it was only possible to make two sections. The slides were examined in random order for the purpose of the study by one observer who was unaware of the source of each section.

A positive diagnosis was made on the basis of all biopsies in 19 out of 55 patients and a suggestive diagnosis in 14 out of 55 patients. In 18 of the 19 positive diagnosis patients the pathological abnormality was present only in a proportion of the biopsies; in 11 of the 19 some of the biopsies were only suggestive. In all 14 patients with a suggestive diagnosis the pathological abnormality was confined to a proportion of the biopsies. A suggestive or positive pleural biopsy diagnosis was made in 26 of 36 (72%) of patients eventually shown to have carcinoma and in seven of eight (88%) of patients with tuberculosis.

The only complications noted were four small pneumothoraces and surgical emphysema in two cases. In patients with thin chest walls it was necessary to occlude the puncture site between biopsies to prevent a pneumothorax. Multiple pleural biopsy is a safe modification of an existing technique and enables a diagnosis to be made which might have been missed if only a single biopsy had been taken.

Cardiopulmonary Function in Patients with Scleroderma

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Cardiopulmonary function has been studied in 25 patients with progressive systemic sclerosis. All patients had a multisystem disease diagnosed clinically. The characteristic skin changes and other features included Raynaud's disease (23), involvement of oesophagus (17), skin ulcers (12), telangiectasia (16), joint stiffness (21), malabsorption (10) and antinuclear factor (15). Lung X-ray showed discrete fibrotic changes in only six patients. We found in 60% of the patients a reduced lung function of restrictive pattern with reduced lung volumes, low elasticity and low static and dynamic compliance. Airway resistance was normal. Very few patients had blood gas disturbances when measured during maximal exercise. There was a high frequency of serious heart involvement, especially malignant arrythmias and a tendency of heart failure mimicking cardiomyopathy. Reduced working capacity was noted in about 90% of the patients. This reduction was due to lung mechanical factors in about 40% and to heart failure in another 30%. A third important factor besides the lung and cardiac involvement, was renal involvement which we found in as many as 30% when measured by Cr EDTA clearance. These three functional disturbances seem to be the main prognostic factors.

Thoracic Involvement and Pulmonary Infection in Hodgkin's Disease

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We have reviewed the case records of the last 122 patients with histologically confirmed Hodgkin's disease who had been seen and treated at Guy's Hospital. Adequate information was obtained on 111 patients. By the Rye modification of the Lukes and Butler classification 15% had lymphocyte-predominant disease, 27% nodular sclerosing, 43% mixed cellularity and 14% lymphocyte-depleted.

At the time of presentation 47% had radiographic evidence of hilar or mediastinal lymphadenopathy and a further 10% have had such lymphadenopathy during their follow-up. At presentation 8% had involvement of the lungs and 5% had pleural effusions. Overall 24% have shown lung involvement and this was most common in lymphocyte-depleted disease where 71% of the patients had a relapse involving the lungs. Three patients who relapsed in the lungs after initial mediastinal radiotherapy had massive glandular enlargement originally.

One patient developed a bronchial carcinoma. There were ten cases of pulmonary infections with radiographic changes, including one of pulmonary tuberculosis. The other nine infections were probably bacterial; eight were associated with active Hodgkin's disease and in seven this was part of the terminal illness with non-responding disease.

Transfer factor was measured in 38 patients and was abnormal in 17. Six of these 17 had pulmonary involvement at the time and two others developed lung involvement over the next six months.

Pulmonary infections appear to be unusual in Hodgkin's disease, except late in the course, and the presence of pulmonary shadowing even with clinical evidence of infection should raise the suspicion of active Hodgkin's disease.

Clinical Features of the Immotile Cilia Syndrome

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The recognition of a human syndrome with congenital ciliary immotility has made possible an evaluation of the role of cilia in the human body. Persons affected by the syndrome have chronic respiratory tract disease since early childhood, absence of mucociliary transport in the airways and, in about half the cases, complete situs inversus and thus may be classified as having Kartagener's syndrome. There is male but not female sterility. Semen samples usually contain normal numbers of live spermatozoa, but sperm motility is absent or severely reduced. Ultrastructural investigations of respiratory tract cilia or sperm tails show defects which in most cases include a lack of dynein arms in the axoneme.

Respiratory tract symptoms include chronic bronchitis and rhinitis, which in most cases can be traced back to early childhood. There is mostly chronic or recurrent sinusitis and often but not always chronic or recurrent otitis. Recurrent pneumonia is common and in childhood or adolescence bronchiectasis is often acquired. In adult life a varying degree of chronic airways obstruction is often but not always present. It can be concluded that the mucociliary transport system of the airways is an important defence mechanism although it is not necessary for the maintenance of life.

Sleep Apnoea in Scheie's Syndrome

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An 18-year-old student (L.M.) presented with a two-year history of day-time somnolence and noisy breathing during sleep. Both he and his elder brother (G.M.) had previously been diagnosed as having Scheie's syndrome, a mucopolysaccharidosis characterized by short stature, micrognathia, fixed flexion deformities of the hands, corneal clouding, hepatosplenomegaly and normal intelligence. Both had raised urinary mucopolysaccharides and undetectable levels of α-iduronidase assayed in cultured fibroblasts.

Sleep studies were performed on both brothers. L.M. had 326 apnoeic episodes during seven hours nocturnal sleep, 317 of which were obstructive apnoea. The mean duration of apnoea was 35 seconds. During apnoea the heart rate fell from a mean of 103 beats/minute to 68 beats/minute ($P < 0.001$) and arterial oxygen saturation fell from a mean of 59% to 35% ($P < 0.001$). During several apnoeic episodes there was EEG evidence of cerebral anoxia.

G.M. had 65 apnoeic episodes, 13 of which were obstructive, 29 central and 23 mixed. The mean duration of apnoea was 23 seconds. Similarly there was a fall in heart rate from 69 beats/minute to 52 beats/minute ($P < 0.001$) and fall in arterial oxygen saturation from 95% to 88% ($P < 0.001$). At the end of several apnoeic episodes G.M. had ventricular extrasystoles.

The significance of the results and further management of these patients was discussed.

Nitrofurantoin-induced Lung Disease in Sweden

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Swedish Adverse Drug Reaction
Committee

More than 1000 reports on suspected adverse drug reactions to nitrofurantoin were received by the Swedish Adverse Drug

Reaction Committee during 1966–76. They constituted about one-tenth of all reports during the latest years of this period.

398 reports on acute pulmonary reactions and 49 reports on chronic pulmonary reactions are presented. In both groups women dominated markedly (approx. 85%). The median age was 59 years in the acute and 68 years in the chronic group. The daily dose of nitrofurantoin was 200 mg in the acute group and 100 mg in the chronic. The first symptoms of the acute pulmonary reactions occurred after an average of seven days of treatment but many of those who had received nitrofurantoin earlier reacted within the first day. Patients with chronic reactions were treated many months (median 17 months) when symptoms first occurred and continued for further three months (median).

Fever, dyspnoea and cough, starting abruptly, were the main symptoms in the acute reactions, while insidious dyspnoea and cough dominated in patients with chronic reactions. Chest radiographs showed lung infiltrations and in 16% of the acute group pleural effusion. Blood eosinophilia was the most common laboratory finding in the acute reactions. Three-quarters of the patients in both groups were admitted to hospital in close relation to the adverse reaction. Nearly half of the patients with acute reactions were free of symptoms within one day after cessation of nitrofurantoin but two elderly women died. Symptoms and radiographic abnormalities persisted for several months in the patients with chronic reactions and four of of them died. Thus acute pulmonary reactions to nitrofurantoin are not unusual in Sweden. Chronic lung disorders are unusual but serious. Early recognition and discontinuation of nitrofurantoin is essential in both types of reactions.

Histopathological Findings and Immune Response to Nitrofurantoin in Drug Intolerance Pneumonitis

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Nitrofurantoin antibodies of the immunoglobulin classes IgG and IgM were found in 18 patients with intolerance reaction to the drug. In one patient nitrofurantoin-specific IgE antibodies were found. IgG and IgM antibodies were also found in control patients treated with the drug but without adverse reaction. Histopathology showed desquamation and swelling of the alveolar epithelium, fibrotic exudate, abundant lymphocytes and microthrombi in small vessels in one patient with acute lung reaction and interstitial fibrosis with thickened atypical alveolar epithelium, lymphocytes and plasma cells in patients with chronic nitrofurantoin lung reaction.

Lung Disease due to Inhaled Tartrazine

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Tartrazine is a commonly used food colour and is added to foods, beverages and medications. Atopic individuals may react to ingestion. Studies have shown a reaction was produced in one-third of allergic patients to whom oral tartrazine was administered. Reactions included weakness, heatwaves, palpitations, blurred vision, rhinorrhoea, feeling of suffocation, pruritus and urticaria.

A non-atopic man developed symptoms six weeks after starting to work as a fork-lift truck driver in a soft drinks factory. He had dyspnoea, chest pain, nasal and eye discharge and loss of voice. Symptoms were slow to resolve on antibiotics. Attempts to return to work led to recurrences of symptoms. Bronchial provocation tests were conducted with ten components used in the factory. Challenge with tartrazine produced symptoms after 50 minutes, with pallor, malaise, shivering, tachypnoea, tachycardia, nasal discharge, injection of conjunctivae and profuse crepitations throughout both lower lobes. The peak expiratory flow rate fell from 540 to 450 litres/minute and persistent nausea required an antiemetic. Signs and symptoms improved over one hour with full resolution in 12 hours. Citric acid produced a similar reaction. These reactions were less severe than those he had at work.

A preliminary questionnaire was given to 197 of 280 workers at a soup powder factory using tartrazine in some products: 15 had respiratory symptoms which they related to their work and 16 others had related nasal symptoms. In 13 a reaction was reported to a substance containing tartrazine, but other components may also have been responsible.

Significant lung disease may occur due to occupational exposure to tartrazine. More detailed epidemiological studies will be needed to assess the extent of the problem.

Mechanical Effects of Early Airway Closure

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This paper concerned the effect on lung mechanics (as reflected in pressure volume studies) of early airway closure. We have compared closing volumes measured by conventional tracer gas techniques, with pressure volume loops recorded on the same day and under the same conditions in individual patients. Our results indicate that distortion of pressure volume loops begins to occur at lung volumes within a few hundred millilitres of the volume at which airway closure is demonstrated by tracer gas methods. It is the intrathoracic pressure changes which are sensed as dyspnoea. These studies throw light on the genesis of the subjective sensation of dyspnoea, in cardiac disease as well as airway obstruction.

Assessment of the Effect of Naturally Acquired Respiratory Infection on Cough Flow–Volume Curves in Normal Healthy Volunteers

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It has been shown that uncomplicated respiratory infections may give rise to changes in pulmonary function in normal volunteers but there is no concensus on the best variables with which to monitor such changes. Coughing is a prominent symptom of respiratory infection but has been little studied. We decided to see if there were any detectable changes in the characteristics of cough during respiratory infection in normal individuals. We recorded cough flow–volume curves and maximum expiratory flow–volume (MEFV) curves at two-week intervals throughout a six-month prospective study in 26 normal healthy volunteers and these measurements were repeated daily when symptoms of infection were present. Thereby a reliable base-line was established and plentiful measurements were obtained during symptomatic periods. In an attempt to mimic the pattern of repetitive coughing the manoeuvre used was a series of three coughs beginning at total lung capacity, uninterrupted by further inspiration, and ending at or near residual volume. The pattern of each cough flow–volume curve was unaltered during infection but both flow and volume characteristics were reduced compared with those obtained during asymptomatic periods. Changes in both flow rates and volumes were of similar order to those observed in the MEFV curve. These changes indicate that cough would be a less effective clearance mechanism during infection. Whilst these changes in coughing did not cause complications in our healthy volunteers a similar impairment of cough in patients with obstructive lung disease may lead to retention of secretions and extension of infection to the lung parenchyma.

Transient Hypoxaemia During Sleep in Patients with Chronic Bronchitis and Emphysema

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Using an ear oximeter to monitor arterial oxygenation we have found that blue and bloated patients with chronic bronchitis and emphysema have episodes of severe hypoxaemia during sleep with actual arterial Po_2 falling to 26 mmHg, but such episodes did not occur in pink and puffing patients with chronic bronchitis and emphysema.

Continuing these studies with both a transcutaneous oxygen electrode, and the ear oximeter, we found transient episodes of mild hypoxaemia during sleep in most pink and puffing patients, but in these the average drop in oxygen saturation was 10% whereas it is more than 40% in the blue and bloated patients. Sleep hypoxaemia may thus contribute to the pulmonary hypertension and secondary polycythaemia which characterizes blue and bloated patients. Such hypoxaemic episodes were less frequent and less severe when these patients breathed low flow oxygen ($P < 0.05$) and the effects of respiratory stimulants during sleep were also described.

These hypoxaemic episodes occur significantly more often in rapid eye movement (REM) sleep than non-REM sleep and we confirm that such episodes are associated with hypoventilation, but do not always indicate apnoea.

Variable Patterns of Blood Gas Response to Controlled Oxygen Therapy in Acute Exacerbations of Chronic Bronchitis and Emphysema

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Retrospective analysis of 157 episodes in 135 patients with chronic bronchitis and emphysema admitted in an acute exacerbation of respiratory failure ($P\text{ao}_2 > 50$ mmHg, $P\text{aco}_2 > 50$ mmHg) between 1961–8 and 1970–6, treated by controlled oxygen therapy, showed that only 111 left hospital alive following the first admission, and of these only 28% survived five years. Death in an admission was not related to $P\text{ao}_2$ when breathing air on admission, but increased with advancing age and severity of acidosis during controlled oxygen therapy, more patients dying if arterial pH was less than 7.25 during treatment. At least two patterns of response of $P\text{aco}_2$ to modest rises in $P\text{ao}_2$ occurred in the first eight hours of controlled oxygen treatment; the classical rise of $P\text{aco}_2$ (> 5 mmHg) occurred in 18, of whom four died; in 21 $P\text{aco}_2$ did not rise, but seven died. Removal of a central hypoxic drive from brain lactacidosis following oxygen administration was unlikely to explain these differences.

Previous studies of hypoxic ventilatory drive show considerable variability between normal subjects, and this, coupled with greater prevalence of profound transient hypoxaemia in sleep in blue and bloated than in pink and puffing bronchitics may contribute to these different patterns. This notion is supported by the variability that we have found in the ventilatory response to constant therapeutic plasma levels of doxapram (2.5 ± 0.1 μg/ml) during progressive isocapnic hypoxia in five normal men, aged 25–46 years, which again implies that human peripheral chemosensitivity varies considerably between individuals in health. Such variability may also account for the different responses in these patients with an acute exacerbation of their chronic respiratory failure.

Survey of Staffing in Thoracic Medicine 1979

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Because of concern about possible failure to maintain the present levels of staffing in thoracic medicine, with consequent fall in standards of care of patients, information about the consultant and senior registrar establishment has been collected by a joint survey made by the BTA, the Thoracic Committee of the Royal College of Physicians and the Thoracic Society. Questionnaires were returned by 98% of those surveyed.

There are currently 394 physicians in thoracic medicine—165 pure thoracic physicians and 229 general physicians with an interest in thoracic medicine. Analysis shows the trend from the former to the latter type of physician. 59% of physicians take part in general medicine and 48% have responsibility for a pulmonary function laboratory. 109 consultants have a senior registrar.

There are 32 senior registrar posts approved for training in thoracic medicine and since many of these rotate with general medical posts there are currently 53 individuals in training. These might be expected to provide about 13 consultants annually. However, because of the peculiar age structure in the speciality, this is far below the numbers required. During the next five years a third of all consultants will have retired and by the end of ten years a half of them will have retired. During the next five years there will be an average of 30 consultant vacancies annually and during the subsequent five years ten annually.

It is concluded that the number of senior registrars at present is quite inadequate to maintain the present level of staffing over the next few years and that a temporary increase in the number of senior registrars must be rapidly attained to ensure a proper standard of care of patients with respiratory disorders.

Theophylline and Terbutaline in Asthma

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Biochemical and pharmacological studies provide a rational basis for the combined use of a β_2-adrenergic agonist and a methylxanthine derivative like theophylline in the treatment of obstructive airway disease. However, sufficient documentation on the possible clinical benefits of such a drug combination are lacking. In our current investigation nine patients with stable chronic obstructive airway disease have been studied to reveal the possible additive effects of terbutaline and theophylline with regard to bronchodilator and side effects.

After the patients' individual pharmacokinetic constants for theophylline disposition had been determined, they were given, randomly and in a double-blind fashion on three separate days, intravenous theophylline to achieve and maintain during the day 0, 40 and 80 μmol/litre of theophylline in plasma respectively. After two, three, four and five hours on theophylline, terbutaline was given intravenously in incremental doses: 1, 2, 4 and 6 μg/kg body-weight respectively. FEV_1, heart rate, blood pressure, tremor, subjective side-effects and theophylline plasma concentrations were regularly registered during the experimental days.

The results showed that both terbutaline and theophylline caused a dose-dependent increase in FEV_1. Pretreatment with theophylline resulted in a bronchodilatation additive to that of terbutaline. Theophylline did not increase the responsiveness of the bronchi to terbutaline. The heart rate increased with increasing doses of terbutaline. Theophylline did not increase the sensitivity of the heart to terbutaline. The interindividual variations were, however, great. Skeletal muscle tremor increased with the dose of terbutaline. Theophylline enhanced the tremorigenic effect of terbutaline. At clinically sufficient bronchodilatation (increase in FEV_1 $>40\%$) the incidence and degree of adverse reactions was lowered by the combination treatment in comparison to either of the two compounds on their own. This was due to the lower dosage of terbutaline and theophyllamine which was required when both the drugs were used in combination.

Aminophylline, Salbutamol and Combined Intravenous Infusions in Acute Severe Asthma

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Twenty-one patients admitted to hospital with acute severe asthma were allocated in a random, single-blind manner, to receive intravenous infusions for 24 hours of either aminophylline or salbutamol or a combination of the two drugs. Infusions were administered by a slow infusion pump with an initial loading dose given over 15 minutes, followed by a continuous lower dose of the drug for 24 hours:

1. Aminophylline 0.285 mg/kg/minute for 15 min (20 mg/minute) followed by 0.014 mg/kg/minute (1 mg/minute).
2. Salbutamol 0.285 μg/kg/minute (20 μg/minute) for 15 minutes followed by 0.057 μg/kg/minute (4 μg/minute).
3. Combined regimen of the above infusions.

In addition each patient received intravenous hydrocortisone (4 g) and potassium chloride (4 g) in 2 litres of 5% dextrose infused over 24 hours, and 35% oxygen given via a Ventimask.

Peak expiratory flow rates showed a significant improvement after 15 minutes treatment with aminophylline and the combined infusion but this was not seen until 60 minutes with the salbutamol infusion. No synergistic bronchodilator effect was seen with the combined infusion. The results show that intravenous aminophylline is superior to intravenous salbutamol in the doses given in the initial treatment of acute asthma and that the combination when given intravenously is not significantly better than aminophylline alone.

Combined Therapy with Theophylline and β_2-Adrenostimulants in Asthmatics

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In vitro studies on human bronchial and skeletal muscle show that the phosphodiesterase enzyme of human bronchial muscle was inhibited at lower concentrations than in skeletal muscle.

Five terbutaline inhalations given at a theophylline plasma concentration of about 15 μg/ml produced nearly the same further bronchodilatation in asthmatics.

Pretreatment with equipotent oral bronchodilating doses of theophylline and terbutaline potentiated the effect of terbutaline by inhalation to the same degree in comparison with pretreatment with equipotent bronchodilating doses of terbutaline given by inhalation. Moderate oral bronchodilating doses of either theophylline or a β_2-adrenostimulant combined with β_2-stimulants by aerosol seem therefore favourable. The choice of the oral treatment depends on the side effects. Theophylline is preferable especially in patients with tremor problems.

Combination of low oral doses of theophylline and β_2-adrenostimulants gave a better bronchodilatation with lower degree of skeletal muscle tremor than a higher dose of β_2-adrenostimulants alone.

High-dose Beclomethasone Aerosol for Severe Asthma

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A group of patients with severe asthma failing to respond to beclomethasone dipropionate aerosol in conventional doses (400–600 μg/day) have been treated with higher doses (up to 2000 μg/day) for periods up to three years or more.

Detailed monthly progress was presented in four such patients over three to five years, including wheezing records, prednisolone and salbutamol consumption, adrenocortical function tests and observations on oral candidiasis. Substantial clinical improvement was achieved with marked reductions in systemic steroid medication. The adrenocortical effects of such treatment during this period are shown in a series of tetracosactrin tests and compared with other tests taken under the influence of prednisolone. It is concluded that beclomethasone aerosol given as described does not suppress adrenocortical function. Side-effects are mainly those of oral candidiasis which seems dose-related but which abates in time with simple mouth-rinsing and occasional local antifungal therapy.

Patients likely to benefit from high-dose therapy are a minority of severe intrinsic steroid-dependent asthmatics who may have complicating bronchitis or emphysema and who fail to respond to conventional beclomethasone dosage. They benefit in terms of clinical status and systemic steroid requirements, though the need for steroid support is not necessarily abolished. The higher dosage of beclomethasone can be conveniently administered in an aerosol containing 250 μg per puff.

BTA Study of Ketotifen in Asthma

A. D. MACKAY

Southampton General Hospital

Oral anti-allergic compounds could benefit asthmatic patients unable to use an inhaler efficiently. Orally administered ketotifen, a cycloheptathiophene derivative, has been shown to inhibit the acute bronchoconstrictor response to inhaled allergen in atopic asthmatic patients. A longer-term comparison of ketotifen and placebo in such patients was reported.

Fifty patients (mean age 36 years) were recruited from 12 centres. All had an FEV_1 above 40% predicted, positive skin tests and a greater than 20% improvement in FEV_1 after inhaled bronchodilator. Patients taking oral corticosteroids were excluded but those inhaling them kept their dosage constant. Sodium cromoglycate was not permitted during the four weeks prior to entry. Patients received each of the following treatment regimens double-blind for one month in random order: (1) ketotifen 1 mg twice a day; (2) ketotifen 2 mg twice a day (3) placebo capsules twice a day. They kept diary cards recording daily symptoms, salbutamol inhaler usage and two PEFR readings thrice daily.

Four patients withdrew because of drowsiness: one on placebo, two on the lower and one on the higher ketotifen dosage. Three patients withdrew because of exacerbations of asthma: two on the lower and one on the higher ketotifen dosage. One patient failed to fulfil the protocol and was excluded. Forty-two patients remained for analysis, 16 of whom were maintained on inhaled steroids. Four of these 42 patients reduced from the higher to the lower ketotifen dosage because of drowsiness.

Values of PEFR showed no statistically significant difference for any treatment period in either the patients taking only inhaled salbutamol as additional therapy or in those on both inhaled corticosteroids and salbutamol. In the 26 patients not already receiving inhaled corticosteroids, ketotifen 2 mg twice a day cause a slight reduction in salbutamol usage from a mean of 24 to 20 puffs/week ($P<0.05$) and improvements in symptom scores for breathing ($P<0.05$).

BTA Survey of α_1-Antitrypsin Deficiency (Progress Report)

D. C. S. HUTCHISON

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This survey will enable cases of α_1-antitrypsin deficiency to be followed up for a number of years in order to establish the natural history of the condition and the influence of α_1-antitrypsin phenotype, sex, smoking habits and other factors upon the prognosis.

A total of 1093 blood samples from patients suspected of having α_1-antitrypsin deficiency have been submitted; 147 were homozygous for type Z and 18 heterozygous for type SZ (the index cases). Blood samples were also obtained from 260 siblings of the index cases, 44 being of type ZZ and 14 of type SZ. Completed clinical questionnaires, lung function data and chest radiographs have been submitted from a total of 137 deficient subjects (119 of type ZZ and 18 of type SZ) upon which the present report was based.

Type ZZ index cases. In this group there were 60 males and 30 females. Of the male cases, 55 were or had been cigarette smokers; only five had never smoked. This 11:1 ratio is substantially greater than the ratio in the general population. Of the females cases 24 had smoked and six had never smoked. Over 80% of the index cases had Grade 3 or 4 dyspnoea (MRC classification). In males, the age of onset of Grade 2 dyspnoea was six years later in those who had never smoked (not significant) and in females 11 years later ($P<0.05$). In both sexes lung function tests showed more severe impairment in those who had smoked, though these subjects were of a younger age. There was little difference between males and females in respect of age of onset of dyspnoea or in lung function tests.

ZZ Non-index cases. Completed questionnaires have been received from 26 type ZZ siblings. There were 12 males and 14 females equally divided between those who had smoked and those who had not. Only four subjects had Grade 3 or 4 dyspnoea.

Type SZ. There were 11 index cases and seven non-index cases. In the index male smokers (seven subjects) the mean age of onset of dyspnoea was 12 years later than in index male smokers of type ZZ ($P<0.001$). The age of onset of dyspnoea in the SZ cases was, however, not significantly different from that found in non-deficient cases of emphysema.

Subjects of the ZZ phenotype have a strong risk of early emphysema. Cigarette-smoking appears to be an additional risk factor. Some ZZ subjects who have never smoked nevertheless develop the disease at an early stage, suggesting other unknown factors. The SZ phenotype apparently carries a much smaller risk.

Inflammatory Bowel Disease and the Lungs

JEANETTE MEADWAY

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Pulmonary disease has been described in association with inflammatory bowel disease. Drug-induced fibrosing alveolitis and pulmonary vasculitis have been described and also apical pulmonary fibrosis resembling that described in ankylosing spondylitis. An increased incidence of bronchiectasis and bronchitis has been reported.

We reviewed 85 cases of ulcerative colitis or Crohn's disease. All case records were obtained and all available chest radiographs (62).

Thirteen patients had a history of pulmonary disease. Two had bronchiectasis. In one, colitis occurred 14 years before respiratory symptoms; the other developed chest symptoms associated with exacerbations of diarrhoea. Five other patients had exacerbations of respiratory symptoms occurring with abdominal symptoms. Two developed pneumonia with an exacerbation of diarrhoea, two others had cough and purulent sputum with exacerbations and one had pleurisy at the onset of Crohn's disease. One patient had apical pulmonary fibrosis and pleural thickening with some calcification persisting after chemotherapy for unproven tuberculosis. Three patients had asthma.

Four patients with respiratory symptoms and ten others had pleural thickening on chest radiographs. Four had associated calcification without any history of tuberculosis. Five others had calcification. No unexpected cases of apical fibrosis were revealed. However, pneumonia, bronchiectasis and bronchitis associated with exacerbations have been demonstrated, suggesting that more than one type of pulmonary disease may be closely linked to inflammatory bowel disease.

Chronic Bronchitis in Sulphite Pulp Factory Workers with Heterozygous α_1-Antitrypsin Deficiency

Leif Rosehall, Gunhild Backman,
Nils Stjernberg and Bo Mikaelsson

University Hospital, Umea

A number of electrophoretically distinct variants of α_1-antitrypsin, the major protease inhibitor in plasma, have been described. About 24 alleles controlling the α_1-antitrypsin variants have been identified so far at the Pi locus. Several of these alleles (PiZ, Pi "–", PiS, PiF) are associated with a low level of α_1-antitrypsin in plasma. It is also known that a low level of α_1-antitrypsin can be associated with lung emphysema, chronic bronchitis, respiratory distress syndromes and non-atopic asthma in children. Environmental factors and smoking could increase the risk of lung emphysema in persons with low α_1-antitrypsin deficiency. We therefore wanted to investigate the effect on the respiratory tract of α_1-antitrypsin deficiency in sulphite pulp factory workers.

The factory investigated was a sulphite pulp factory combined with a paper mill. The employees were exposed to SO_2 and Cl_2. There were 532 employees and, 519 (97.6%) participated. Blood samples were collected and serum stored at −20°C until analysed. The serum samples were analysed by starch gel electrophoresis, crossed immunoelectrophoresis and iso-electrofocusing in the pH range 4–5. Seronorm protein was used as a standard.

Serum levels and phenotyping of α_1-antitrypsin was performed in 518 persons. 473 (91.2%) had the normal M_1 or M_2 phenotypes; 20 (3.9%) had M_1Z or M_2Z (heterozygous for the Z-allele); 19 (3.7%) had M_1S or M_2S, six (1.2%) had M_1F or M_2F. Thus 45 (8.8%) had heterozygous α_1-antitrypsin deficiency, corresponding to 2.3% in a control group ($n = 884$) from northern Sweden. The serum levels of α_1-antitrypsin were lower for Z, S and F alleles than for the normal M_1, M_2 alleles. The sex and age distribution were the same in the whole population as in those with α_1-antitrypsin deficiency. Those with α_1-antitrypsin deficiency were also evenly distributed over different working places.

Symptoms of chronic bronchitis (productive cough daily during three months per year for two consecutive years) were found in 46 (8.9%) persons in the whole population. This figure is higher than in the surrounding area. The patients with α_1-antitrypsin deficiency had a tendency towards higher frequency of chronic bronchitis than those with the normal M_1, M_2 alleles (15.6% and 8.2% respectively). This difference was, however, not significant ($P = 0.1$). Dynamic spirometry showed no difference between the persons with α_1-antitrypsin deficiency and those with M_1, M_2 alleles.

FUTURE MEETINGS OF THE BTA

The list below gives details of future meetings, both arranged and provisionally planned. I hope this will prevent the clashing of dates with meetings arranged by other societies.

1 February 1980	Jointly with the Thoracic Society. Royal Free Hospital, London. Preceded by meeting of the Thoracic Society on 31 January at the same venue which BTA members are invited to attend
9–11 April 1980	Jointly with the Welsh Thoracic Society. University of Swansea
3–6 September 1980	Jointly with the Norwegian Thoracic Society. Lillehammer, Nr. Oslo, Norway. *Note that this is a change of date.* The cost will be approximately £22 per day for full pension. It is hoped to negotiate a cheaper rate for members wishing to stay a week.
Late January 1981	Jointly with the Thoracic Society. A two-day meeting in London
6–9 May 1981	Jointly with the Europe Region International Union Against Tuberculosis and the Chest, Heart and Stroke Association. Bournemouth.
30 June–3 July 1982	Jointly with the Thoracic Society. University of York
27–30 June 1983	Churchill College, University of Cambridge
24–27 June 1985	Churchill College, University of Cambridge

Further details of these meetings can be obtained from Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA.

FUTURE MEETINGS OF THORACIC SOCIETY

31 January–1 February 1980	Jointly with the British Thoracic Association. Royal Free Hospital, London. BTA members are invited to attend meeting of the Thoracic Society on 31 January 1980
3–4 July 1980	Durham University
Late January 1981	Jointly with the British Thoracic Association. A two-day meeting in London
3–5 July 1981	St Andrews University. Jointly with the Scottish Thoracic Society
30 June–3 July 1982	Jointly with the British Thoracic Association. University of York

PAPERS INVITED

The British Thoracic Association invites papers for presentation at the Joint Meeting with the Thoracic Society on 1 February 1980. Summaries of 200–300 words should be submitted to the Honorary Secretary, Dr G. Anderson, Newport Chest Clinic, 129 Stow Hill, Newport, Gwent NPT 4GA, by 26 October 1979. Papers are also invited for the meeting with the Welsh Thoracic Society and abstracts should be sent to the Honorary Secretary by 25 January 1980.

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BOOK REVIEWS

Lung Biology in Health and Disease, 9. Chronic Obstructive Pulmonary Disease

Thomas L. Petty

New York: Marcel Dekker. 1978. Pp. xvi + 270. Price SFr 70

This short book is the first clinical volume in this important series. Whereas earlier volumes have been scholarly reviews of the scientific background to respiratory medicine, this volume, which is based mainly on the considerable experience of the University of Colorado, concentrates on practical identification and care of patients with chronic airway disease and is directed at 'all physicians, nurses and therapists who care for sufferers of chronic obstructive pulmonary disease'.

The book is dedicated to the late A. L. Barach who provides chapters on Physiotherapy and the Adaptive Function of Hypercapnia. Through a long career Dr Barach made outstanding contributions to the care of these patients—laying the foundations for avoiding carbon dioxide narcosis by controlled oxygen therapy, introducing the concept of directly measuring expiratory slowing, postulating that a raised $P\text{CO}_2$ could reduce the work of breathing and experimenting with helium–oxygen breathing, all before the Second World War! His major theme in this book is on the improvement of diaphragmatic function by encouraging the bending forward posture. He supports the use of physiotherapy that aims to deflate the lung (slow, deep breathing, assistance with negative pressure) and feels that present-day emphasis on the hazards of decrease in lung volume and bronchial closure has been too great.

The remaining chapters cover other aspects of identification, prognosis and treatment. The chapter on drugs provides long lists of available commercial preparations but little guidance as to how these should be used, and their effects assessed, in practice. Burrows contributes a very brief chapter on Course and Prognosis which only serves as an introduction to his important work on this subject. Chapters on respiratory failure and rehabilitation are profusely illustrated with pictures of patients walking through hospital corridors, reading magazines, gardening, etc., but the accompanying tables and discussions are often too diffuse to serve as a practical guide to management. The sections on the role of bronchial infections and on pulmonary function are extremely brief. Although the book contains interesting material, the chapters vary greatly in their depth of coverage and the result is a book which is not consistently successful either as a coherent account of clinical management or as a critique of current views on the pathogenesis and treatment of chronic airflow obstruction.

N. B. PRIDE

Neonatal Respiration: Physiological and Clinical Studies

L. B. Strang

Oxford: Blackwell Scientific. 1978. Pp. xii + 316. Price £14.50

When I first saw the title of this book, I was faintly disappointed, but the subtitle, together with the actual contents, has made me revise my attitude entirely. It is excellent to be able to read a consecutive account of the distinguished work on absorption of lung liquid which has been undertaken by Professor Strang and his team at University College Hospital.

Professor Strang not only looks with great insight on the perinatal situation but he also goes on to consider the neonatal period. One might have liked to have seen a little emphasis on the rationale for positive pressure ventilation in the resuscitation of the newborn infant at birth but it is probable that the author considers this a battle entirely won.

The reappearance and re-advertising of Vandid, re-named as Clairvan (ethamivan), for neonatal resuscitation does not fill me with the same confidence. I am told that this drug, which is dangerous in the infant who is beyond the last gasp at birth, is still available on many resuscitation trolleys in places less distinguished than UCH.

It is much to be hoped that this book will become required reading for SHOs and registrars in neonatal units and (one might add) for consultants. The book is a splendid declaration that applied physiology is fundamental to the care of both the well and the sick neonate and it is most impressive to note that very little of it could have been written 25 years ago. A last and pleasing reflection is to observe that the author uses words which are effective and part of every-day speech, particularly his own. One feels it will want re-writing in the next five to ten years but this is as it should be in a subject which is developing so fast.

K. W. Cross

Lung Biology in Health and Disease, 10. Pathogenesis and Therapy of Lung Cancer

Curtis C. Harris

New York: Marcel Dekker. 1978. Pp. xx+ 762. Price $59.50

This is the tenth book in this series and in common with the others it is beautifully produced with high-quality illustrations and large open type. It is expensive but provides the reader with a lot for his money.

The book is a series of reviews of the growing points in research into lung cancer. Each is comprehensive, up-to-date and supremely well referenced. The balance reflects the American belief that the solution to man's ills lies in basic research. There are four main sections, the first of which deals with environmental and host factors. This brings together all the epidemiological data on tobacco and occupation in lung cancer and succeeds in making it both digestible and interesting. This section can be strongly recommended. The second and largest section is entitled Respiratory Carcinogenesis in Experimental Animals. This is difficult reading and often comes close to being a laboratory worker's cookery book. However, scanning the recipes is valuable since it gives the general reader a clear insight into the formidable difficulties of this sort of work and warns him against facile attempts to apply the results of these experiments to man. The research worker will doubtless find this section invaluable. The third section joins pathology with carcinogen metabolism in man. In many ways this is the best part of the book. The difficulties of histological classification and the inter-relationships of the different cell types and their progression to malignancy are well discussed and the illustrations are superb. The chapter on carcinogenesis in human tissues is particularly stimulating and suggests exciting possibilities for the identification of smokers with a predisposition to lung cancer. The final section deals with tumour biology, reviewing a number of basic concepts which are well known to oncologists but unfamiliar to most chest physicians and surgeons. Tumour doubling time, labelling index and the cell cycle are concisely explained and this should be particularly valuable to the general reader. Finally, occupying only 7% of the book, is a chapter on diagnosis, staging and treatment. This can hardly be comprehensive since surgery, radiotherapy, chemotherapy and immunotherapy are each allowed only a page or two. Given these limitations the chapter is surprisingly successful.

Overall the book has two major defects. From the point of view of a practising clinician the balance is wrong. The laboratory animal wins a too convincing victory over the patient with the disease. From the point of view of the research worker the book is a triumph today and will be out of date tomorrow; it is unlikely that any of the research reviews will last more than two years. Nevertheless, the book can be strongly recommended as one of the best in this series. It brings together a huge and diverse body of knowledge in a way that should be widely accessible. No clinician will change his management of lung cancer as a result of reading this book but he will gain a much deeper understanding of the disease.

Duncan Geddes

Dictionary/Reference Guide for Respiratory Therapy

J. Owen Krasowski

Chicago: Year Book Medical Publishers. 1977. Pp. x + 114. Price not stated

This small paper-backed book is, as its title states, an alphabetical collection of basic respiratory terminology, common and some not so common. It is essentially a practical little book. It is very elementary in its approach as it is intended for those beginning to take an interest in this field of care—that is respiratory therapists in the United States, physiotherapists in the United Kingdom, technicians and students.

All the definitions are completely oriented to the respiratory world and no indications of any other meaning is given, i.e. weaning = gradual disconnection from mechanical ventilation, and clapping = a form of chest percussion.

In order to keep the book small and easily portable many of the definitions are very brief and because of this they are, I think, in some cases somewhat misleading, i.e. digitalized = increased systole. In some instances the definitions, at least as the terms are used in the United Kingdom, are incorrect, i.e. haemostasis = localized rupture of an artery or vein.

As this book is written in America some of the terms are related only to the USA and some words in the dictionary are obviously more commonly used in America than here.

Some of the definitions are given only in terms of a further medical statement, i.e. interventricular heart block = bundle branch block, which may not clarify the situation for those for whom this book is intended.

There is an error in the definition of carbon monoxide uptake where carbon dioxide is used incorrectly in the place of carbon monoxide.

At the end of each section there is a useful space for the addition of further terms and notes.

At the end of the book there are 28 appendices giving in a short space a quantity of extremely valuable information clearly and concisely assembled. These appendices cover symbols, abbreviations, medical prefixes, conversion factor of all types, ventilator types, anaesthesia tubes for infants, children and adults, normal values for pulmonary function tests to mention only a few.

It is obviously difficult in such a small volume to cover all the terms used in respiratory therapy at length but those starting in this field will, I think, find it a very useful little volume, particularly the final section, and it will stimulate its users to seek further information on a number of topics.

ELIZABETH CORNWELL

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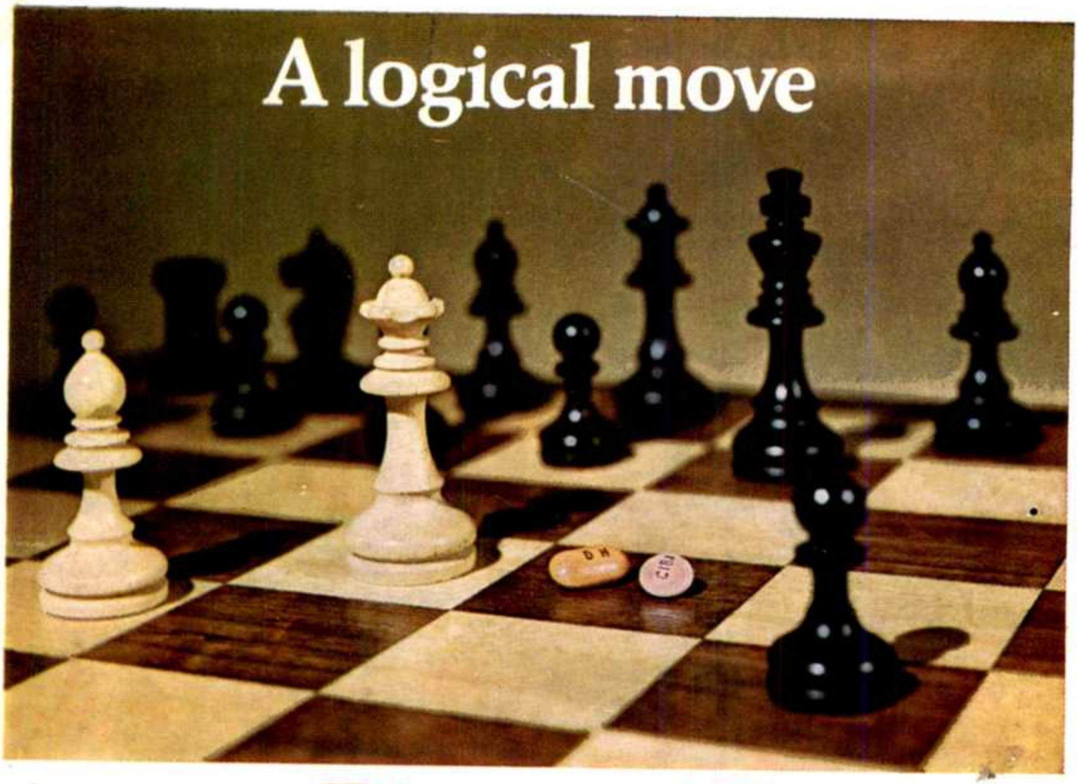

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